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Department of Pathological Physiology

M.V. Osikov, A.A. Ageeva, K.S. Savchuk, L.V. Vorgova

PRACTICE GUIDE ON GENERAL PATHOPHYSIOLOGY FOR STUDENTS OF MEDICAL DEPARTMENT

Learning guide

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as learning guide for students of HE with specialization in general medicine

Under general editorship of M.V. Osikov, Professor

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Reviewers:
E.V. Markelova – Head of the Department of Pathological Anatomy of Federal State Budgetary Education Institution Pacific State Medical University of the Ministry of Health of Russia, Doctor of Medical Sciences, Professor.
O.V. Korpacheva – Head of the Department of Pathological Anatomy of Federal State Budgetary Education Institution Omsk State Medical University of the Ministry of Health of Russia, Doctor of Medical Sciences, Assistant professor.
E.L. Kazachkov – Head of the Department of Pathological Anatomy and Forensic Medicine of the FSBEI HE SUSMU of the Ministry of Health of Russia, Doctor of Medical Sciences, Professor.
Z.V. Vozgova – Head of the Department of foreign languages with course of Latin at Federal State Budgetary Education Institution of Higher Education South Ural State Medical University of the Ministry of Health of Russia, Doctor of Education, Assistant professor.
Authors:
M.V. Osikov - Head of the Department of Pathological Physiology of the FSBEI HE SUSMU MOH Russia, Doctor of Medical Sciences, Professor.
A.A. Ageeva - Assistant of the Department of Pathological Physiology, FSBEI HE SUSMU MOH Russia.
K.S. Savchuk - Assistant of the Department of Pathological Physiology, FSBEI HE SUSMU MOH Russia.
L.V. Vorgova - Associate Professor of the Department of Pathological Physiology of the FSBEI HE SUSMU MOH Russia, Ph.D., Associate Professor

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The manual is intended for students of higher educational institutions studying in the specialty 31.05.01 General Medicine.

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Pathophysiology is then taught to a medical student
that it puts the mind of the future doctor in order

M.V. Osikov

FOREWORD

The manual contains methodological developments for preparation for practical classes in the discipline Pathophysiology and their conduct among students of the medical faculty. All materials were prepared by the staff of the Department of Pathophysiology, taking into account the requirements of the Federal State Educational Standard of Higher Education in the specialty 31.05.01 General Medicine (specialist level), approved by Order No. 95 of the Ministry of Education and Science of Russia dated 09.02.2016. The textbook is based on a course of lectures on general pathological physiology for students of the pediatric faculty and includes 15 teaching and monitoring modules (lessons) on general nosology and typical pathological processes. Each lesson indicated:

- key questions (correspond to the questions to prepare for the exam),
- theoretical part with a discussion of the features of the course of pathological processes in pediatric practice (causes and conditions, mechanisms of occurrence, course and outcome, principles of diagnosis and therapy).

Conducting the practical part of the lesson, solving test tasks and situational tasks is aimed at forming the foundations of rational thinking and effective behavior of a doctor in specific clinical situations, the ability and readiness to assess morphological and functional changes in the body for solving professional problems, mastering the methodology and technology of medical practice based on systemic (pathophysiological) analysis, the ability to transform theoretical knowledge into elements of professional activity.

The textbook is not exhaustive; to prepare for practical exercises, it is necessary to use the information of the lecture course and educational literature on pathophysiology. At the end of the manual there is a list of basic and additional literature in the study of the discipline Pathophysiology. In addition to those indicated, other modern textbooks and guidelines on pathophysiology can be used.

The authors will be grateful for useful advice, comments, recommendations (e-mail: patfiz_chelsma@mail.ru).

Head of Pathological Physiology Department
FSBEI of Higher Education "South Ural State
Medical University"
Ministry of Health of the Russian Federation
Doctor of Medical Sciences, Professor M.V. Osikov

Practical lesson 1. Introduction. Subject and tasks of pathophysiology. Historical stages of pathophysiology development. Modeling of pathological processes.

Key questions of the lesson

1. Pathological physiology. Subject, purpose, tasks, its place among other medical disciplines. The importance of pathophysiology in medicine.

2. Methods of pathological physiology. experimental modeling of diseases: its types, possibilities and limitations.

Pathological physiology. Subject, purpose, tasks, its place among other medical disciplines. The importance of pathophysiology in medicine

Pathophysiology as a science has officially existed for more than 200 years. The relationship between normal and pathological processes in the body, structural and functional changes in the disease was pointed out by Fernel (J. Fernel, 1497-1558) in the treatise "De naturali parte medicinae" (1542) (Figure 1.1), Varandes (Iohannes Varandes) in the treatise "Opera omnia" (1618). However, the term "pathological physiology" was one of the first to be used in 1791 by Professor A. F. Hecker of the University of Erfurt (textbook "Fundamentals of Pathological Physiology"), and then L. Gailliot repeated it in 1819. in the textbook "Pathologie general et physiologie pathologique" ("General pathology and pathological physiology"). Rapid development of experimental medicine at the beginning of the XIX century. It contributed to the division of general pathology into pathological anatomy and pathological physiology. In the USSR in the 1924/25 academic year, on the initiative of A.A. Bogomolets and S.S. Khalatov, the departments of general pathology were renamed into the departments of pathological physiology, and the scientific specialty "pathological physiology" was allocated.

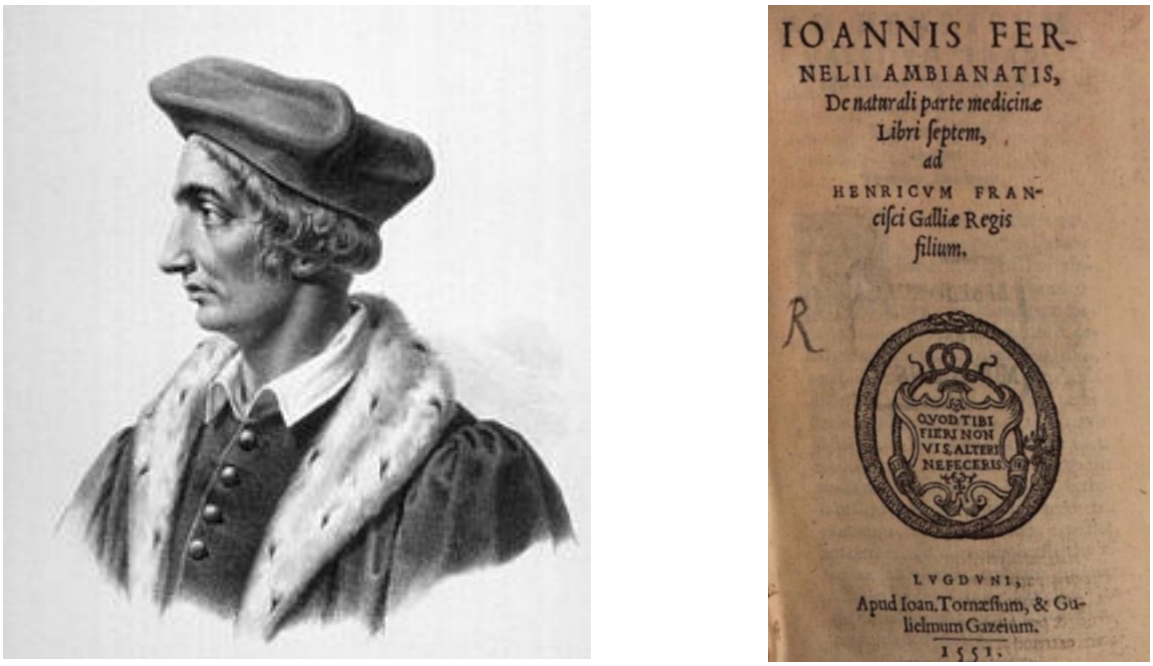

Figure 1.1 J. Fernel (1497-1558), the treatise "De naturali parte medicinae" (1542)

The founder of the Russian pathophysiology and the St. Petersburg school of pathophysiology is Viktor Vasilyevich Pashutin (1845-1901). In 1878 Pashutin published "Lectures on general pathology (pathological physiology)", and later "Course of general and experimental pathology-pathological physiology" (1885-1902). A great contribution to the development of Russian and Soviet pathophysiology was made by representatives of the St. Petersburg school (V.V. Pashutin, P.M. Albitsky, E.S. London, N.N. Anichkov, S.S. Khalatov, P.N. Veselkin, I.R. Petrov), the Moscow school (A.I. Polunin, A.B. Fokht, G.P. Sakharov, A.D. Speransky, A.D. Ado, A.M. Chernukh, G.N. Kryzhanovsky, V.A. Negovsky), Kharkiv school (S.D. Kostyurin, A.V. Reprev, D.E. Alpern), Kiev school (V.K. Lindeman, V.V. Podvysotsky, A.A. Bogomolets), Tomsk school (P.M. Albitsky, A.V. Reprev, P.P. Avrorov, D.I. Timofeevsky, D. I. Goldberg), etc. N.G. Speransky made a great contribution to the study of children's age pathology.

The history of the South Ural School of Pathophysiology begins in 1944, it was created on the basis of the Kiev Medical Institute evacuated to Chelyabinsk. The Department of Pathophysiology was headed by a learner

of Academician A. A. Bogomolets Raphael Aronovich Dymshits (1898-1981), who headed the department until 1970. Then the Department of pathophysiology was headed by a learner of R.A. Dymshits G.K. Popov (from 1970 to 1996), L.V. Krivokhizhina (from 1996 to 2016), M.V. Osikov (from 2016 d.).

Synonyms of the term "pathological physiology" are "experimental pathology" (first used by F. Mazhandi and K. Bernard, in Russia – V.V. Pashutin), "general pathology" (used in English-speaking countries), "physiopathology" (used in French-speaking countries). Clinical pathophysiology arises and develops along with classical pathophysiology, which was formed as an experimental science. Clinical pathophysiology study the patterns of the occurrence and development of diseases in clinical conditions using modern highly informative harmless methods (biochemical, electrophysiological, radiation diagnostics, etc.). It is preferable to use the term "pathophysiology" instead of the phrase "pathological physiology", which includes three Greek words: pathos (disease, suffering, pathology), physis (nature, essence), logos (teaching, science). Thus, pathophysiology is the science of the essence of the disease, the vital activity of the sick organism. Like any other science, pathophysiology has a goal, objectives, and methods. At the present stage of development of medical science, the following definition is generally accepted:

Pathophysiology – the science that studies general patterns the emergence, development and completion of diseases, principles and methods of diagnosis, treatment and prevention of diseases.

The purpose of pathophysiology is to clarify the causes and mechanisms of disease development, develop principles and methods for their diagnosis, treatment and prevention.

Tasks of pathophysiology:

1. Find out the etiology of pathological processes, syndromes, diseases
2. To study the pathogenesis of pathological processes, syndromes, diseases
3. Investigate the reactivity of the patient's body
4. Study the mechanisms of recovery (sanogenesis)
5. Develop principles for the diagnosis, treatment and prevention of diseases

Methods of pathological physiology. experimental modeling of diseases: its types, possibilities and limitations

Methods of pathophysiology are numerous – this distinguishes it from other medical sciences and at the same time requires knowledge of any methods when solving specific problems: morphological, biochemical, biophysical, immunological, microbiological, etc. The main method of pathophysiology is pathology modeling. Its founders are French scientists, François Magendie and Claude Bernard, and in Russia – V.V. Pashutin. All methods of pathophysiology can be divided into three groups:

1. methods of modeling pathology
2. methods for assessing changes in the patient's body or in the model
3. methods of interpretation of the received information and creation of a pathology complete picture.

Modeling of pathology can be carried out in two ways: in an experiment and by mathematical modeling (in silico). Mathematical modeling involves the creation of an abstract model – it is usually a computer program that describes the structure and function of the body as a whole or more often its parts in order to study changes in it in any pathology and find ways to correct them. modern computer technology, including supercomputers, is used for modeling in silico. This can be used to model, for example, the aging of the body, various arrhythmias, etc. conditions, as well as develop medicines, vaccines. experimental modeling is based on the reproduction of pathology in a living object to study the causes and mechanisms of its development and develop methods of correction. The object of the experiment can be animals (Figure 1.2), humans, isolated organs, tissues, and cells. Depending on the conditions, in vitro and in vivo experiments are distinguished. According to the duration of the experiments, they are classified into acute and chronic. Recently, more and more priority is given to experiments on tissue cultures, isolated cells, isolated organs, guided by ethical considerations. Various laboratory animals are used in the experiment (mice, rats, guinea pigs, rabbits, dogs, pigs, monkeys, etc). Adequate selection of laboratory animals for a particular experiment is of great importance. Thus, allergic reactions, light desynchronosis, avitaminosis are better modeled on guinea pigs, tumors, the effect of anatoxins, the infectious process – on mice, neuroses - on dogs and monkeys, atherosclerosis - on rabbits, etc. Not all diseases can be reproduced in animals are not amenable to modeling mental illness, some types of tumors, gout, bronchial asthma, etc. diseases.

The following main approaches are used in the experiment:

1. Shutdown-removal or damage of an organ (for example, a model of diabetes mellitus when removing the pancreas);
2. Inclusions – the introduction of any substances into the body (for example, a model of thyrotoxicosis with the introduction of thyroid hormones);
3. Irritations – for example, a model of bradycardia in vagus nerve irritation;

4. Isolated organs – for example, experiments on isolated animal hearts to study the causes and mechanisms of heart failure;

5. The method of tissue culture – for example, the isolation and cultivation of lymphocytes to study their secretory activity in any disease.

Figure 1.2 A laboratory animal in a thermal injury simulation device

To assess changes in the body or isolated cells, organs, any methods can be used depending on the task – histological, cytological, biochemical, genetic, immunological, microbiological, etc.

Statistical methods, methods of analysis and synthesis are used to interpret the obtained information. They allow us to summarize the obtained data and establish causal relationships between disorders at different levels of organization – from the whole organism to cellular and molecular.

The importance of pathophysiology in medicine is the integration of fundamental theoretical disciplines (anatomy, histology, biology, biochemistry, physiology, microbiology, immunology) with clinical disciplines (therapy, surgery, obstetrics and gynecology). This is the combined estimate of changes in the body with the disease, the construction of a causal relationship between them, highlighting the causal factor and the conditions of emergence of the disease, understanding the mechanism of disease development and justification of effective measures of therapy (directed at the cause or mechanisms of disease development) and prevention. relatively speaking, pathophysiology is the alpha and omega of medicine, since pathophysiology begins with the idea of the disease (etiology, pathogenesis) and ends with it (etiotropic and pathogenetic therapy, principles of prevention, etc.). In this regard, even V. V. Pashutin called pathophysiology "the philosophy of medicine". "Pathophysiology is the foundation of medical professional intelligence" (from the preamble to the WHO constitution) - we can argue thanks to the integrative position of pathophysiology in medicine.

The importance of pathophysiology in the system of higher medical education is reduced to the formation of medical thinking – that is, the ability to solve medical problems (diagnosis, treatment, prevention) based on data about the patient and his illness, that is, the ability to "apply natural science at the patient's bedside" (S.P. Botkin).

Pathophysiology as an academic discipline includes three sections:

1. General nosology (general etiology, general pathogenesis, sanogenesis)
2. Typical pathological processes (inflammation, fever, hypoxia, tumor growth, shock, etc.)
3. Private pathophysiology (pathophysiology of organs and systems).

General nosology and typical pathological processes make up the general pathophysiology.

Practical lesson 2. General nosology. Etiology, pathogenesis. Damage levels. Disease, its definition, main components of the disease: pathological reaction, pathologic process, pathological condition. Stages, clinical outcome.

Key questions of the lesson

1. General nosology as a section of pathophysiology.
2. Basic concepts of general nosology: pathological reaction, pathological process, pathological condition. Examples. The concept of the typical pathological process.
3. Norm, health, transitional state of the organism between health and disease (pre-illness). Examples.
4. Disease: definition, stages of the disease, outcomes. Specific and non-specific, general and local manifestations. The concept of the syndrome.
5. Recovery: mechanisms, the role of protective, compensatory and restorative forces. The concept of sanogenesis.
6. Etiology: term, its definition. The role of causes and conditions in the onset and development of diseases. The theoretical and practical purpose of etiology. Classification and characteristic of etiological factors. Iatrogenic diseases.
7. Pathogenesis: term, its definition; initial, leading links of pathogenesis. Examples. Causal relationships in pathogenesis: "vicious circles", its role and examples.
8. The value of studying etiology and pathogenesis. The concept of etiotropic, pathogenetic, symptomatic, sanogenetic, replacement therapy.

General nosology as a section of pathophysiology

Nosology (Greek nosos - disease, logos - doctrine, science) is a section of pathology that forms general ideas about the disease, which is based on its etiology and pathogenesis. It includes the following parts:

1. nosology itself;
2. general etiology;
3. general pathogenesis;
4. general sanogenesis.

Nosology itself develops the basic concepts of pathology, the nomenclature and classification of diseases. The basic concepts of nosology include the following: norm, health, pre-illness, disease, syndrome, pathological reaction, pathological process, pathological condition.

Basic concepts of general nosology: pathological reaction, pathological process, pathological condition. Examples. The concept of the typical pathological process

The constituent elements of the disease are a pathological reaction, a pathological process, a pathological condition, and a syndrome.

A pathological reaction is an inadequate and biologically inexpedient short-term response of the body to the effects of conventional or pathogenic environmental factors. Examples include increased sweating in the cold, coronary angiospasm and an attack of angina pectoris with irritation of the biliary tract, pathological reflexes.

A pathological process is a natural sequence of compensatory and pathological reactions arising from the action of damaging environmental factors and leading to structural and functional changes in tissues. Examples of pathological processes: inflammation, fever, hypoxia, shock, tumor growth, etc.

Properties of a typical pathological process:

- phylogeneticity: a typical pathological process was formed and fixed in the course of evolution, it proceeds stereotypically in different classes of animals (for example, inflammation in fish, amphibians, reptiles, birds, mammals);
- polyetiology: the reasons for a typical pathological process can be many (for example, inflammation is caused by physical, chemical, biological factors - phlogogens);
- monopathogenicity: the mechanism of development of a typical pathological process is the same regardless of the cause and localization in the body (inflammation proceeds the same in the stomach with gastritis and in the meninges with meningitis);
- autochthonousness, equifinality: a typical pathological process that began under the influence of a cause (for example, a carcinogen in malignant tumors or a phlogogenic factor in inflammation) then proceeds spontaneously (autochthonous), regardless of the causative factor being found in the body, goes through all stages up to the final (equifinality).

Thus, unlike a disease, a pathological process can have several causes (the disease always has one main cause); it may not be accompanied by a disability, the symptoms of the pathological process are not of the same type as in the disease, but directly depend on its localization (inflammatory process in the myocardium, stomach, lung has various symptoms). In addition, the disease is usually a combination of pathological processes (with myocardial infarction, hypoxia, acidosis, inflammation, etc. are observed).

A pathological condition is a slow (long-term) pathological process. Examples: a scar after tissue damage, a condition after amputation of a limb, a condition after tooth extraction, the result of a violation of intrauterine development (defects of the upper lip, hard palate).

Norm, health, transitional state of the organism between health and disease (pre-illness)

There are two main approaches used to define the concept of norm: biostatistical and adaptation-individual. In accordance with the biostatistical approach, the norm is the most frequently found value of any parameter in the population (for example, normal values of blood pressure, heart rate, the number of erythrocytes in the blood, etc.). This approach is commonly used in clinical practice and is reflected in reference books on clinical laboratory diagnostics. The biostatistical approach to the norm takes into account such characteristics of a person as race, age, sex, but doesn't introduce the full range of possibilities of the genotype.

According to the adaptation-individual approach, the norm is considered as a reflection of the optimal vital activity of a given individual at a certain point in time in a specific situation (for example, a change in blood pressure in an adult during the day: during sleep, wakefulness, exercise, after emotional stress or drinking coffee). Thus, we can talk about the relativity of the norm - situational (the example above with blood pressure), historical (change in the norm of indicators as a reflection of the acceleration of the population), geographical (for example, the number of red blood cells in the inhabitants of the plains and mountainous areas).

According to the recommendations of WHO experts (1948), health is a state of complete physical, mental and social well-being, not just the absence of diseases or physical handicaps.

One of the main criteria for health is the ability to work. "Health is an existence that allows participation in various types of social and work activities" (A.D. Ado). In accordance with the laws of thermodynamics, health can be considered as a state in which the level or rate of increase in entropy in the body is minimal. "Health is a state of complete harmony of individual organs" (V.V. Pashutin). The factors influencing the formation and maintenance of human health were identified by WHO experts in the 80s of the twentieth century and are conditionally divided into 4 groups. Among them, lifestyle (50–55%) and the state of the environment (up to 25%) have the maximum impact on health, followed by heredity (15–20%) and the level of medical support (up to 15%). The ratio of these factors depends on gender, age, place of residence and individual characteristics of a person.

Thus, in view of the above, we can give the following definition health is a relatively perfect and stable form of life that provides optimal mechanisms of adaptation to the environment and allows you to have a functional reserve for its change.

From the standpoint of preventive medicine, it is important to detach the concept of pre-disease. Examples of pre-disease are conditions such as obesity, hypersensitivity (sensitization) to a specific antigen, stress, neuroses, precancerous conditions (dysplasia of the epithelium of the bronchi, intestines). These conditions may not lead to the development of the disease itself or, on the contrary, end with a transition to diseases such as arterial hypertension, coronary heart disease, atherosclerosis, allergic diseases, and malignant tumors. The state of pre-disease can be detected during stress tests (physical activity, pharmacological tests, glucose loading, etc.), which reveal a decrease in the effectiveness of the body's adaptive mechanisms.

Pre-illness (premorbid state) is a transitional state of the body between health and illness, which is characterized by a change in the reactivity of the body, excessive stress of sanogenetic mechanisms, can turn into a disease or end with the restoration of structure and functions.

Disease: definition, stages of the disease, outcomes. Specific and non-specific, general and local manifestations. The concept of the syndrome

The ability to get sick is a key property of living organisms. If we don't have disease, we would die much more often. There are two types of programs are launched in case of illness:

1. compensatory (adaptation at the maximum level), "physiological measure against the disease" according to I.P. Pavlov;

emergency (breakage) - the inclusion of mechanisms, which healthy body doesn't have.

It is very difficult to differentiate these two types of programs in a clinical setting; moreover, during the course of the disease, compensatory programs can switch to emergency. "There are difficulties when you have to distinguish in the aspect of the disease in general medicine: what is a result of damage and what is a result of the body's resistance to this damage. These two categories of phenomena are very confused. It is the purpose of science and a talented doctor to separate them and understand what is a true disease and what is a physiological

measure against a disease" (I.P. Pavlov). We can say that the disease starts where the zone or adaptation limit ends (Figure 2.1).

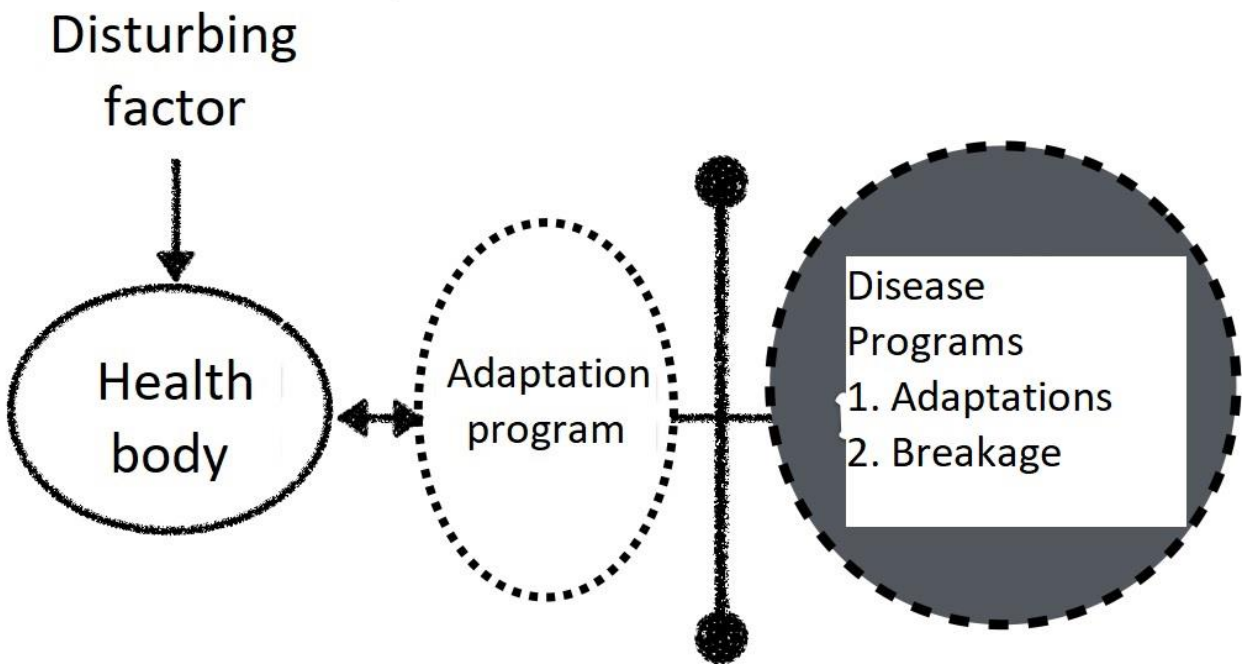

Figure 2.1 Disease as reflection of adaptation's limit

The disease is an enforced, unstable form of life,

● which is raised in response to the action of damaging environmental factors or as a result of the implementation of a genetic defect,

● is characterized by the development of a complex of structural and functional compensatory and emergency (pathogenic) changes,

● is manifested by the limitation of biological and social capabilities of a person.

Classification of diseases

1. By duration

- lightning fast, fulminant (minutes - hours); example: fulminant hepatitis;
- acutest (up to 4 days); example: cholera;
- acute (5-14 days); example: acute pneumonia, acute heart failure;
- subacute (15 - 40 days); example: subacute disseminated tuberculosis;
- chronic (months, years); example: chronic heart failure, chronic respiratory failure

2. Periods of illness

- onset (latent, incubation)
- height of the disease (disease proper)

general and local signs of the disease (symptoms) appear, which can be nonspecific (characteristic of many diseases - weakness, headache, fever), specific (characteristic of a certain group of diseases - shortness of breath, pain in the epigastric region), pathognomonic (which is a diagnostic sign specific disease); complication - a pathological process or condition that may occur against the background of the underlying disease (for example, hypertensive crisis in hypertensive disease)

- disease outcomes:

recovery - restoration of disturbed structures and functions of a sick organism, adaptive capabilities and working capacity; recovery can be complete when there are no traces of the disorders observed in the disease, and incomplete with the preservation of residual symptoms of the disease (for example, bacterial carriage after an infectious disease); incomplete recovery can turn into a relapse (return or worsening of symptoms of the disease) or into a chronic form of the disease

transition to a chronic form of the disease, which is characterized by alternating periods of remission (temporary disappearance or weakening of symptoms) and relapses (re-development or aggravation of symptoms of the disease after a period of remission)

death - the process of termination of the body's vital activity, including the following successive stages: preagonia, terminal pause, agony, clinical death, biological death.

A syndrome is a collection of symptoms united by pathogenesis. Examples: hemorrhagic syndrome, anemia, heart failure.

Recovery: mechanisms, the role of protective, compensatory and restorative forces. The concept of sanogenesis

Sanogenesis (lat. Sanos - health, Greek genesis - origin, emergence) is a doctrine of the mechanisms of recovery. There are urgent and long-term mechanisms of recovery. Urgent mechanisms include protective reflexes (coughing, sneezing, vomiting), stress response (activation of the nervous and endocrine systems leading to the mobilization of the body's capabilities), the inclusion of reserve capabilities of organs. Examples of long-term healing mechanisms are acquired immunity, increased tissue volume under stress (hypertrophy, hyperplasia).

Etiology: term, its definition. The role of causes and conditions in the onset and development of diseases. The theoretical and practical purpose of etiology

Classification and characteristic of etiological factors. Iatrogenic diseases

Etiology (Greek aitia - reason, logos - doctrine) - the doctrine of the causes and conditions of disease.

Learning etiology allows us to answer the question why do diseases arise. The cause of the disease is a factor that directly causes the disease and gives it specific features. Without a cause, disease doesn't occur under any circumstances. There are exogenous (physical, chemical, biological, social factors) and endogenous (disorders in the genotype) causes of the disease (Table 2.1).

Table 2.1 Pathogenic factors

Disease's causes	Samples
Physical factors	Mechanical (stretching, compression, impact, falling) Thermal (general and local hypothermia, hypothermia) radiation electric current high and low ambient pressure, gravity free state sound waves (noise), ultrasonic, ultraviolet rays, laser radiation
Chemical factors	Acids, bases, salt of heavy metals, toxic gases, free radicals, pharmaceutical products
Biological factors	Microorganisms (bacteria, viruses, fungus), protozoaires, helminths and its waste products, snake venom, bee venom
Social factors	Psychic trauma, mental stress, iatrogeny, inanition

A disease condition is a factor contributing to, inhibiting, or modifying the effect of a disease cause. Examples of disease conditions are an increasing air humidity with a decreasing ambient temperature, malnutrition (conducive to exogenous conditions), immunodeficiency in children and the elderly (conducive to endogenous conditions), rational, balanced nutrition, good patient care (obstructive exogenous conditions), human species immunity to pneumonia of cattle, plague of dogs and other infectious diseases of animals (interfering endogenous conditions).

The etiological factor is the purpose of etiotropic therapy (for example, the use of antimicrobial agents for infectious diseases) and prevention - a set of measures aimed at preventing its effects on the body (antiseptics and asepsis, vector control as prevention of infectious complications). In addition, the suppression of the effects of conditions conducive to the occurrence of diseases (use of clothes, rejection of bad habits) and the potentiation of the effects of conditions that prevent the occurrence of diseases (rational nutrition) can be attributed to preventive measures.

Thus, the disease is caused by a combination of unequal factors. In this regard, several concepts have upraised, which explain the disease oneset; the most famous of which are conditionalism and monocausalism. Conditionalism (from Lat. Conditio - condition) is the doctrine of the etiology of diseases, according to which they are caused by the effect on the body of a set of equivalent factors, and it is impossible to single out the main factor among them. Monocausalism (from Latin causa - cause) is the doctrine of the etiology of diseases, according to which they are caused by the influence of one factor (cause) on the body, and all other factors are indifferent. Both concepts of disease etiology are wrong. At present, it is generally accepted that among the etiological factors, the main one (the cause of the disease) is distinguished, all the rest are conditions - facilitating, preventing or modifying the effect of the cause.

In clinical practice, due to develop effective measures for therapy and prevention of diseases, it is extremely important to distinguish the main etiological factor and conditions of the disease. Until now, it is impossible to do this for some diseases - multifactorial, polyetiologic diseases (arterial hypertension, atherosclerosis, etc.). This position is erroneous and is associated with the lack of our knowledge about the etiology of these diseases, which over time, as the results of clinical and experimental studies accumulate, will be corrected, including due to the disintegration of diseases into new subspecies with separate causes.

It is generally accepted that the likelihood of developing a disease is determined, firstly, by the properties of the etiological factor ("grain" of the disease), and secondly, by the properties of the organism itself ("soil" for the onset of the disease), that is, its reactivity. Thus, the development of the disease is the result of the interaction of the organism itself and the etiological factor: from the development of the disease to its absence, which is clearly manifested during the epidemic of respiratory diseases, when some people do not develop the disease.

Pathogenesis: term, its definition; initial, leading links of pathogenesis. Examples

Causal relationships in pathogenesis: "vicious circles", its role and examples

Pathogenesis (Greek pathos - suffering, illness, genesis - origin, emergence) is the doctrine of the general patterns (mechanisms) of the occurrence, development and completion of diseases and typical pathological processes, the principles and methods of their pathogenetic therapy.

The study of pathogenesis allows us to answer the question of how, in what way does the disease develop? Pathogenesis is a chain of events united by a causal relationship:

1. the initial link of pathogenesis is an etiological factor, it can trigger a disease and its further effect on the body is optional (inflammation, tumor growth) or the etiological factor is constantly present in the body during a disease (microorganisms in infectious diseases); changes that are observed in the body after exposure to an etiological factor are called pathogenetic factors of the first order, they are sources of other changes - pathogenetic factors of the second, etc. order.

2. the leading (key) link in pathogenesis is a pathogenetic factor that determines the further development of pathology and is the goal of pathogenetic therapy. For example, the formation of biologically active substances - mediators in inflammation, a decrease in the BCC in blood loss. The use of antihistamines for inflammation or transfusion of blood, plasma, plasma replacement solutions after blood loss are examples of pathogenetic therapy.

3. a vicious circle (circulus vitiosus) is formed when one link in pathogenesis is a factor in strengthening or maintaining another link. An example of a vicious circle is, after acute blood loss, a decrease in the oxygen capacity of the blood (hypoxia), which leads to a decrease in oxygen supply to all tissues, including the myocardium, which causes acute heart failure, a decrease in the contractile function of the heart and, as a consequence, aggravates systemic hypoxia (Figure 2.2).

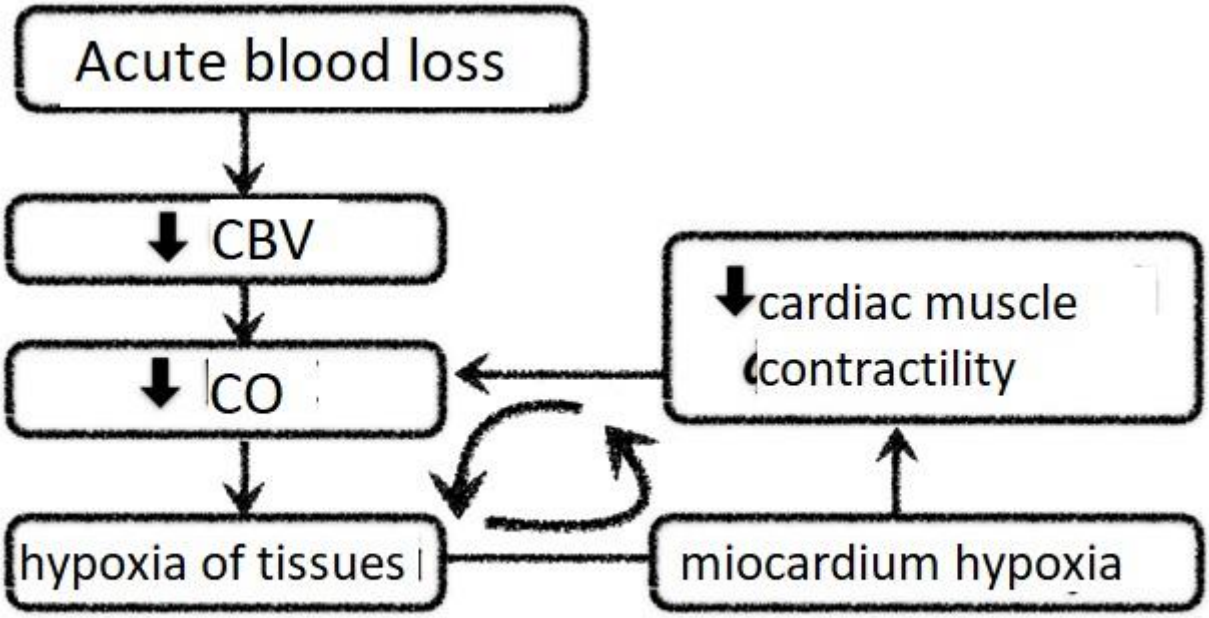

Figure 2.2 Vicious circle under acute blood loss. Decreasing CBV is the leading link of pathogenesis.

Factors of pathogenesis reflect a complex of events leading to structural and functional changes in the body, which are manifested by symptoms - signs of the disease. Signs of the disease can be clinical, laboratory, instrumental. In addition, disease symptoms can be local and general, specific or non-specific. For example, with inflammation, local signs (redness, edema, local fever, pain, dysfunction) and general signs (weakness, fatigue, headache, neutrophilic leukocytosis, increased ESR, dysproteinemia) can be observed.

The value of studying etiology and pathogenesis. The concept of etiotropic, pathogenetic, symptomatic, sanogenetic, replacement therapy

Sanogenetic therapy is aimed at activating compensatory reactions and processes during the disease, for example, the use of immunostimulating drugs for chronic infectious diseases or immunosuppressants for autoimmune diseases (rheumatoid arthritis). Substitution therapy involves the use of factors that eliminate the deficiency or absence of any components in the body, for example, the use of insulin in patients with diabetes mellitus, thyroxine in hypothyroidism, enzymes in pancreatic insufficiency).

Practical lesson 3. Reactivity and resistance of the body and its significance in pathology. The constitution of the body. The influence of pathogenic environmental factors on the body.

Key questions of the lesson

1. Reactivity of the body: definition, types and forms of reactivity. Examples. Methods for assessing the patient's reactivity.
2. Factors of the external and internal environment that affect reactivity. The importance of studying reactivity.
3. Body resistance: definition, non-specific and specific resistance factors, examples of their violations.
4. The constitution of the body: definition, classification. The dependence of reactivity on the human constitution.

Reactivity of the body: definition, types and forms of reactivity. Examples. Methods for assessing the patient's reactivity.

Reactivity (latin: reactio-counteraction) – this property of the whole organism responds to changes in vital activity to the influence of factors of the external or internal environment.

There are types and forms of reactivity (Table 3.1).

Table 3.1 Reactivity types

Reactivity types	Examples
Generic	animals are not affected by certain human diseases (botulism does not occur in dogs and cats), humans are not threatened by dog plague and foot-and-mouth disease in cattle
Collective	age (children and the elderly are more susceptible to infectious diseases due to immaturity or involution of the immune system organs), sex (resistance to blood loss is higher in women, and to physical activity in men, gout occurs more often in men, and rheumatoid arthritis in women), constitutional (asthenic more common gastric ulcer, hyperstenic such as arterial hypertension, atherosclerosis)
Individual	different severity of symptoms among people during an infectious disease epidemic (influenza, acute respiratory viral infection, etc.)
Physiological	reactivity of a healthy person: the release of digestive enzymes in response to food entering the gastrointestinal tract, increased breathing and heartbeat during exercise, perspiration when the external temperature rises
Pathological	the body's response to the pathogenic factors action, the disease reactions complex
Specific	immune response reactions: the antibodies production, the specific T-lymphocytes formation on the antigen introduction
Non-specific	reactions of innate immunity to the antigen introduction (phagocytes activation and increase in the number them, complement activation), hypersecretion of mucus, saliva, vasospasm in blood loss

Reactivity forms determine the body's reaction severity to the influence of any factors, they include normergia (the body's adequate reaction to the influence of the factor), hyperergia (excessive reaction to the stimulus), hyperergia (weak reaction to the stimulus), anergia (the body's lack of reaction to the influence of the factor), dysergia (atypical, perverted reaction).

Body resistance: definition, non-specific and specific resistance factors, examples of their violations.

The concept of reactivity is closely related to the concept of **resistance** (lat. resisteo-resistance) – the body's resistance to the pathogenic factors action (Table 3.2).

Table 3.2 Resistance types

Resistance type	Examples
Passive	anatomical structures (skin, mucous membranes, blood-brain barrier) physiological mechanisms (HCl secretion in the stomach) antibodies transfer during blood and plasma transfusions
Active	phagocytosis, antibody synthesis, formation of specific T-lymphocytes, etc. immune reactions mechanisms of thermoregulation, increased heart rate, respiratory rate

Natural (primary, hereditary)	immunity to own antigens, to bovine plague, immunity of sickle cell anemia patients to malaria
Acquired (secondary, induced)	after the get over an infectious disease to their causative agent, after the introduction of vaccines and serums, resistance to physical exertion after training
Specific	resistance to a specific pathogen (for example, a microorganism or its toxin) after vaccination or a specific serum injection
Non-specific	resistance to any pathogens

Cross-resistance – formation of resistance to several external factors, even those that have never acted on the body. For example, resistance to acute respiratory viral infection after hardening, resistance to hypoxia, being in high-altitude conditions after physical training, etc.

Reactivity and resistance are related, but do not always change unidirectionally. Thus, during anesthesia during dental surgery, they reduce the reactivity and at the same time increase the resistance of the body to traumatic damage.

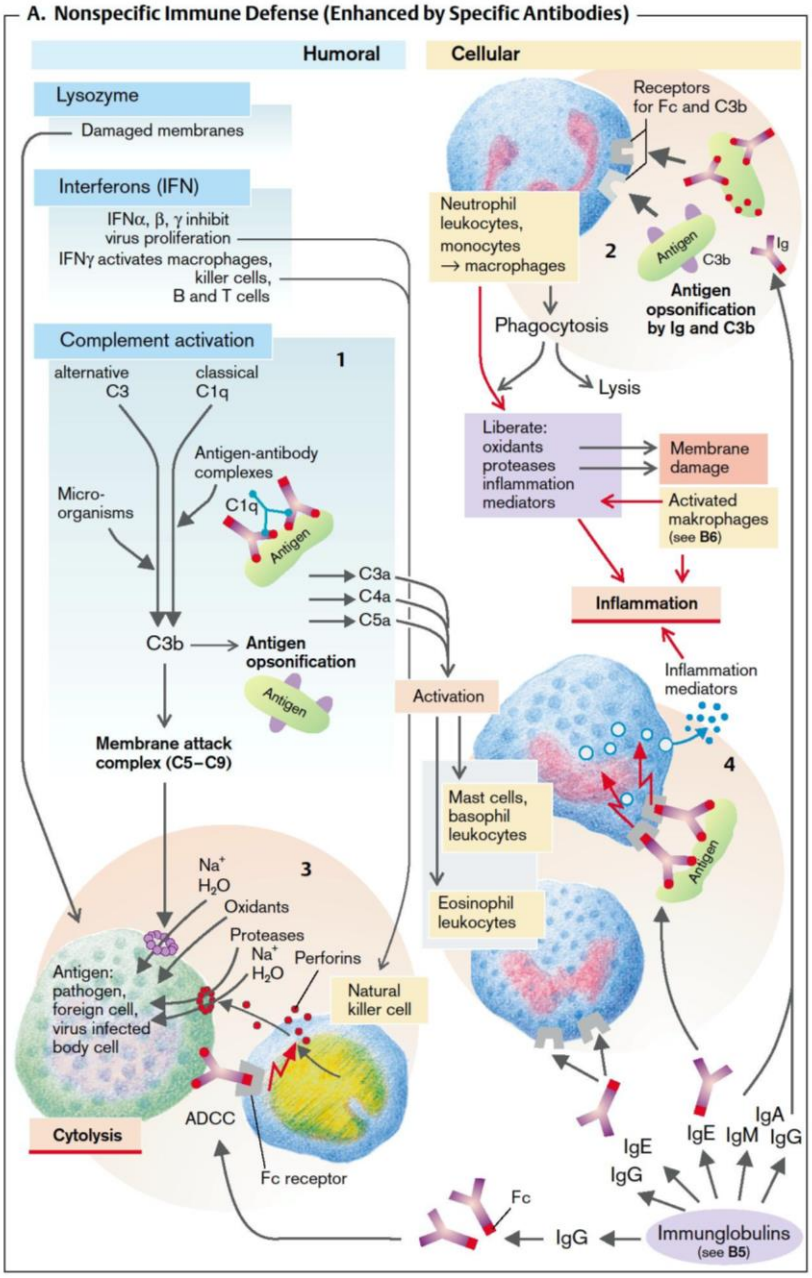

Figure 3.1 Immune defense as an example of reactivity and resistance of the body. (Inserts from S. Silbernagl, F. Lang: Color Atlas of Pathophysiology, 2 ed., New York, 2010, Thieme.)

Practical lesson 4. Cell damage

Key questions of the session:

1. Cell damage: definition of the concept, cause, cell damage. Examples of specific and non-specific manifestations of cell damage.
2. Mechanisms of disruption of energy supply to cells. Mitochondrial cytopathies, examples.
3. Mechanisms of damage to cell membranes. Significance of the process of free radical oxidation in cell damage. Mechanisms of oxidative stress. Antioxidant defense system.
4. Mechanism of short and long term compensation in response to cell damage. Examples.
5. Syndrome of ischemia - reperfusion: etiology, pathogenesis, manifestations. Examples.
6. Mechanisms of cell death. Comparative characteristics of apoptosis and necrosis. Examples of intensification and insufficiency of apoptosis in pathology.

Cell damage: definition of the concept, cause, cell damage. Examples of specific and non-specific manifestations of cell damage

A cell is a structural and functional unit of tissues, organs and the body as a whole, which has its own metabolism, the ability to divide, and maintain homeostasis. Any cell can be in the following states, including after exposure to a damaging factor (Figure 4.1):

1. Homeostasis - functioning within the normal range (characterized by normal morphological parameters, the concentration of electrolytes in the cytoplasm, and other indicators) under conditions of exposure of the cell to various signals and factors;
2. Adaptation - a complex of adaptive factors after exposure to a damaging factor; includes such conditions as hypertrophy, hypotrophy, hypoplasia, hyperplasia, etc., may result in a transition to homeostasis or cell damage; if adaptation is exhausted, and restoration of structure and function is not achieved, cell damage occurs;
3. Cell damage - a complex of reversible changes that occur after exposure to a damaging factor when adaptive capabilities are exceeded (morphological equivalents - dystrophy, metaplasia, dysplasia);
4. Cell death - irreversible cessation of the cell's vital activity by starting a special program (apoptosis) or as a result of lethal damage (necrosis).

The structural and functional characteristics of the cell and intracellular adaptive mechanisms are studied by cytology, histology, normal physiology, biophysics, biochemistry, and other disciplines, the field of study of pathology (pathomorphology and pathophysiology), damage and cell death.

Cell damage is a typical pathological process,

- stimulating in response to damaging environmental factors,
- characterized by the development of a complex of compensatory and emergency programs,
- manifests itself by changes in the structure, metabolism and function of the cell.

Etiology of cell damage

1. Physical factors
- mechanical (impact, stretching, rupture, compression)
- thermal (temperature high or low)
- radiation (ionizing, ultraviolet)
- electric current
- changes in the osmotic pressure of the interstitium

2. Chemical factors
- free radicals
- change in concentration of O_2, CO_2
- aggressive substances (acids, alkalis, salts of heavy metal, ethanol)
- specific cytotoxins (cyanides, arsenic salts)
- medicines

3. Biological factors
- exogenous (microorganisms and products of their vital activity)
- endogenous (autoantibodies, autoaggressive T-lymphocytes, enzymes, hormones)
- genetic disorders

Basic mechanisms of cell damage

1. Violation of the energy supply of the cell
2. Damage to cell membranes

3. Dysregulation of intracellular processes
4. Genetic disorders
Cell damage traits
There are systemic manifestations of cell damage (Figure 4.1).

Manifestation	Cause
Fever	Release of endogenous pyrogens (interleukin-1, tumor necrosis factor-alpha, prostaglandins) from bacteria or macrophages; acute inflammatory Response
Increased heart rate	Increase in oxidative metabolic processes resulting from feve
Increase in number of leukocytes (leukocytosis)	Increase in total number of white blood cells because of infection
Pain	Various mechanisms, such as release of bradykinins, obstruction, pressure
Presence of cellular enzymes in extracellular fluid	Release of enzymes from cells of tissue
Lactate dehydrogenase	Release from red blood cells, liver, kidney, skeletal muscle
Creatine kinase	Release from skeletal muscle, brain, heart
Aspartate aminotransferase	Release from heart, liver, skeletal muscle, kidney, pancreas
Alanine aminotransferase	Release from liver, kidney, heart
Alkaline phosphatase	Release from liver, bone
Amylase	Release from pancreas
Aldolase	Release from skeletal muscle, heart
Troponins	Release from heart

1. Reversible changes
● cell swelling
● swelling of organelles (mitochondria, endoplasmic reticulum, Golgi apparatus)
● disintegration of the rough endoplasmic reticulum
2. Irreversible changes
● cytoplasmic membrane: rupture
● nuclei: karyopycnosis (shrinkage, condensation), karyorexis (decay), karyolysis (dissolution of chromatin)
● mitochondria: double membrane rupture, fragmentation, calcification, formation of myelin figures
It is impossible to unambiguously identify morphological or pathochemical signs of irreversible cell damage. Usually, two events indicate irreversible changes:
1) the inability to restore mitochondrial function after damage (adenosine triphosphate synthesis),
2) deep disturbances in the structure and function of membranes.
Signs of irreversible changes:
● cardiomyocytes - no contractions, specific changes on the electrocardiogram, increased concentration / activity in plasma of enzymes alanine aminotransferase, lactate dehydrogenase
● hepatocytes - an increase in the concentration / activity in the plasma of the enzymes aspartate aminotransferase, lactate dehydrogenase
● β-cells of the islets of Langerhans - decreased insulin production → diabetes mellitus
● any cells - an increase in plasma concentration of K^+
3. Specific changes
● under the action of a certain pathogenic factor on various cells (an increase in osmotic pressure in any cells leads to water accumulation, swelling up to cytolysis, uncouplers of oxidation and phosphorylation in any cells lead to a decrease in adenosine triphosphate synthesis)
● under the action of various damaging factors on a certain type of cells (erythrocytes respond to the effects of many factors by cytolysis, myocytes - by contracture)

4. Non-specific changes

● stereotyped changes under the influence of different damaging factors on different cells - protein denaturation, acidosis, increased membrane permeability, etc.

Mechanisms of disruption of energy supply to cells. Mitochondrial cytopathies, examples

1. Starting factors:

- a decrease in the supply of O_2 (cell hypoxia)
- a decrease in the intake of oxidation substrates (glucose, fatty acids, etc.)
- dysfunction (damage) of mitochondria - a decrease in the activity and / or the number of enzymes involved in the synthesis of adenosine triphosphate

2. Mechanisms:

- disruption of adenosine triphosphate synthesis (during glycolysis, Krebs cycle, conjugation reactions of oxidation and phosphorylation)
- violation of adenosine triphosphate transport in the cell (more than 25 enzyme systems, including adenosine triphosphate / adenosine diphosphate - translocase, creatine phosphokinase)
- disruption of adenosine triphosphate utilization in the cell due to a decrease in the activity of adenosine triphosphatase enzymes:

• Myosin adenosine triphosphates → violation of muscle contractions

• Na^+, K^+ - adenosine triphosphates → change in the concentration of Na^+ and K^+ in the cell

• Ca^{++} - adenosine triphosphatase → change in the concentration of Ca^{++} in the cell

3. Consequences:

dysfunction of ion channels (consume up to 70% of all adenosine triphosphate synthesized in the cell) → violation of the concentration of electrolytes in the cell

1) impaired function of Na^+, K^+ - adenosine triphosphatase → ↑ $[Na^+]$ ↓ $[K^+]$ in the cell →

• ↑ $[H_2O]$ → cell swelling → cytolysis

Morphological sign: hydropic dystrophy

• depolarization of the cytoplasmic membrane → dysfunction of neurons, myocytes

for example, with a decrease in the blood supply (ischemia) of the myocardium → the contractility of cardiomyocytes, the formation of resting and action potentials (electrogenesis) are disturbed, which is recorded in the form of specific changes on the ECG

2) dysfunction of Ca^{++} - adenosine triphosphatase → ↑ $[Ca^{++}]$ in the cell →

(normal ratio of calcium concentration in the cytoplasm and in the interstitium is 1: 10000)

• activation of intracellular enzymes

protein kinases, proteases, endonucleases, phospholipases

• dysfunction of mitochondria

uncoupling of oxidation / phosphorylation processes, decrease in adenosine triphosphate synthesis, heat release

• dysfunction of muscle cells (impaired relaxation)

→ contracture of skeletal muscles, cardiac arrest in systole

Damage to cell membranes (cytoplasmic membrane, mitochondrial membranes, endoplasmic reticulum, etc.)

can be provided by several mechanisms:

• activation of free radical oxidation processes
• activation of intracellular enzymes (phospholipases)
• stretching and rupture of membranes (when cells and organelles swell)
• action of immune factors (complement)
• the action of detergents (substances that build in and damage the membrane)

Mechanisms of damage to cell membranes. Significance of the process of free radical oxidation in cell damage. Mechanisms of oxidative stress. Antioxidant defense system

Free radicals are atoms, ions or molecules that have an unpaired electron in their outer orbital, which leads to their high reactivity.

The processes of free radical oxidation (FRO) in the cell reflect the balance between the activity of prooxidant systems and the activity of antioxidant systems. The activation of FRO processes in the cell is due to an increase in the activity of prooxidant systems and / or a decrease in the activity of antioxidant systems. Emerging data indicate that ROS play roles in the initiation and progression of cardiovascular alterations associated with hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, chronic heart failure, and sleep apnea.

In all cells of our body, O_2 is used during 4-electron reduction with the formation of water for the synthesis of adenosine triphosphate by enzymes of the mitochondrial respiratory chain. During the one-electron reduction of O_2, a superoxide anion radical is formed, which is a source of other radicals, including the reactogenic hydroxyl radical $OH^{\bullet}$ (Figure 4.1).

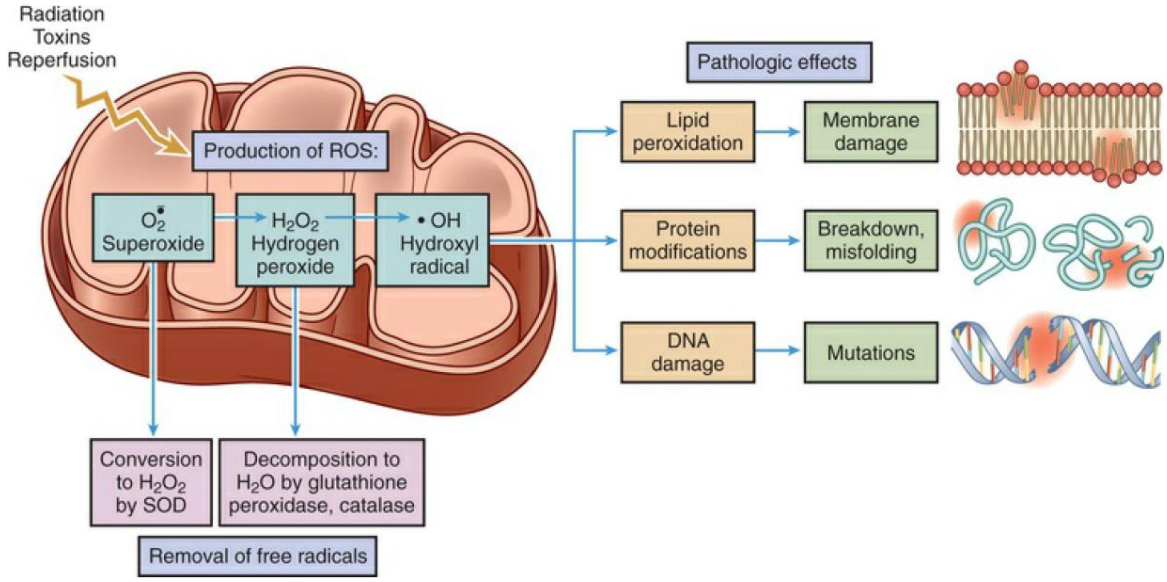

Figure 4.1 Role of Reactive Oxygen Species in Cell Injury. The production of reactive oxygen species (ROS) can be initiated by many cell stressors, such as radiation, toxins, and reperfusion of oxygen. Free radicals are removed by normal decay and enzymatic systems. ROS accumulate in cells because of insufficient removal or excess production leading to cell injury, including lipid peroxidation, protein modifications, and DNA damage or mutations. SOD, Superoxide dismutase. (Adapted from Kumar V, Abbas A, Aster J: Robbins & Cotran pathologic basis of disease, ed 9, Philadelphia, 2015, Saunders.)

1. Starting factors:

1) an increase in the activity of prooxidant systems (formation of free radicals)

• exogenous factors

ozone, metals of variable valence - Fe, Cu

ionizing radiation, ultraviolet radiation

• endogenous factors

activation of free radical producing cells: phagocytes, endothelial cells, hepatocytes

2) a decrease in the activity of antioxidant systems (inactivation of free radicals)

Antioxidants are substances that reduce the formation or inactivate free radicals:

vitamin C, tocopherol, carotenoids, ubiquinone, enzymes - superoxide dismutase, catalase, peroxidase, plasma proteins - ceruloplasmin, haptoglobin, alpha-1-acid glycoprotein

2. Mechanism:

Increased formation of $OH^{\bullet}$ and other radicals

3. Consequences of activating FRO processes:

- activation of lipid peroxidation → damage to the cytoplasmic membrane and membranes of organelles (violation of integrity, electrical stability)

$LH + OH^{\bullet} \rightarrow L^{\bullet} + H2O$

$L^{\bullet} + O2 \rightarrow LOO^{\bullet}$ (peroxyl radical)

$LOO^{\bullet} + LH \rightarrow L^{\bullet} + LOOH$ (lipid hydroperoxide)

- "crosslinking" of proteins through SH-groups → inactivation of proteins, formation of aggregates

for example, cataract of the lens with aging (accumulation of free radicals)

- rupture of deoxyribonucleic acid molecules in the nucleus and in mitochondria → mutations (malignant tumors)

Dysregulation of intracellular processes

Signal transmission to the cell occurs through the interaction of substances (ligands) with cellular receptors in two ways:

1. Hydrophilic ligands (cytokines, adrenaline, acetylcholine, insulin, etc.)

interaction with a receptor on the surface of the cytoplasmic membrane

→ secondary messengers → activation of protein kinases

→ changes in biochemical reactions, metabolism, membrane permeability, gene transcription

2. Lipophilic ligands (steroid hormones, thyroxine)

interaction with a receptor inside a cell (cytoplasm or nucleus) → ↑ activity of transcription factors → triggering gene transcription → protein synthesis

Localization of dysregulation of intracellular processes

- at the receptor level
- at the level of secondary messengers
- at the level of biochemical reactions inside the cell

1. At the receptor level

- a decrease in the number of receptors (damage by radicals, microbial toxins, decreased synthesis)
- violation of the structure, qualitative changes in receptors (for example, with an increase in cholesterol in the membrane)
- change in receptor sensitivity (blockade by autoantibodies)

2. At the level of secondary messengers

accumulation of excess cyclic adenosine monophosphate in the cell

e.g. cholera vibrio → intestinal epithelium → activation of adenylate cyclase

→ ↑↑↑ cyclic adenosine monophosphate → release of Na and H_2O into the intestinal lumen → decrease in BCC

→ hypohydration of the body

3. At the level of biochemical reactions in the cell

Relatively speaking, enzymes in the cell act on the substrate (S1), leading to the formation of another substrate (S2). With a decrease in the activity (absence) of the enzyme, the S1 substrate accumulates in the cell and the amount of the S2 reaction product decreases. This is observed, for example, in diseases of storage (glycogenosis, sphingolipidosis).

Genetic disorders

1. Starting factors:

- ionizing radiation, ultraviolet radiation
- chemical agents (free radicals, alkylating compounds)
- viruses
- activation of endonucleases

2. Mechanisms of genetic disorders:

- gene mutations
- decreased activity of vital genes (for example, enzyme synthesis)
- increased activity of pathogenic genes (for example, protooncogenes)
- transfection of foreign deoxyribonucleic acid (viruses)
- violation of the mechanisms of deoxyribonucleic acid repair

3. Consequences:

- a decrease in the synthesis of vital proteins (for example, insulin and its receptors in diabetes mellitus)
- synthesis of pathogenic proteins (for example, oncoproteins and the formation of a malignant tumor)
- induction of apoptosis

Mechanism of short and long term compensation in response to cell damage. Examples

1. Functional footprint (urgent mechanisms)

- compensation for energy deficiency in the cell

activation of mitochondrial enzymes, activation of glycolysis, use of creatine phosphate, etc.

- compensation for damage to the cytoplasmic membrane

activation of cell antioxidant systems

- compensation for genetic disorders

activation of the deoxyribonucleic acid repair system

- synthesis of heat shock proteins (chaperonins, ubiquitins)

2. Structural footprint (long-term mechanisms)

- atrophy (decrease in cell volume) → decrease in functional activity

→ saving resources → reducing the degree and scale of damage

- hypertrophy (increase in cell volume) and hyperplasia (increase in the number of cells)
- dystrophy - morphological reflection of metabolic disorders

dysproteinosis, lipidosis, dyspigmentosis, thesaurismosis

Syndrome of ischemia - reperfusion: etiology, pathogenesis, manifestations. Examples

Ischemia (decreased blood flow to tissue, oxygen and substrate delivery) is the most common cause of cell damage due to decreased adenosine triphosphate production. As described above, adenosine triphosphate deficiency leads to disruption of the work of energy-dependent cellular systems, primarily ion pumps (which leads to an imbalance of Na^+, K^+, Ca^{++}, cell edema), decreased protein synthesis, depletion of glycogen stores, accumulation of lactic acid, and intracellular acidosis.

For example, with ischemia of the heart muscle, cardiomyocytes stop contracting 60 seconds after the cessation of blood flow. However, the loss of contractile function does not mean cell death, no significant structural changes are observed, since internal energy resources in the form of creatine phosphate are used. If myocardial ischemia continues for 5-10 minutes, the depletion of adenosine triphosphate stores causes reversible changes in metabolism, structure, and function of the myocardium, which are restored after normalization of blood flow: enzymes of the mitochondrial respiratory chain are activated, glucose becomes the predominant substrate for oxidation, rather than fatty acids, glycolysis is activated , in the cell and its organelles (mitochondria, endoplasmic reticulum), edema is observed, the concentration of water, sodium and chloride increases and the concentration of potassium decreases.

If myocardial ischemia lasts more than 10 minutes, then the damage becomes irreversible and necrosis occurs. Irreversible damage is associated with the activation of free-radical oxidation processes, the synthesis of ROS, which trigger damage to cell membranes (lipid peroxidation). This is manifested by severe mitochondrial edema, extensive damage to plasma membranes, and lysosomal edema. There is a leak of cellular enzymes into the extracellular space. A massive influx of calcium into the cell can lead to death through necrosis and apoptosis.

The restoration of blood flow can lead to the repair of cells in case of reversible damage. However, under certain circumstances, restoration of blood flow in pre-ischemic tissues, paradoxically, aggravates and accelerates damage. As a result, further cell damage occurs in the tissues up to irreversible changes and death. This complex of tissue changes is called ischemia-reperfusion syndrome. The clinical significance of ischemia-reperfusion syndrome is associated with the aggravation of tissue damage in myocardial infarction and cerebral infarction after the restoration of blood flow in the cardiac or cerebral arteries, respectively.

There are several mechanisms that lead to cell damage as a result of reperfusion in ischemic tissues.

1. Excessive synthesis of free radicals, their sources are:

- mitochondria - ubisemiquinone of the respiratory chain
- an increase in the concentration of hypoxanthine, the metabolism of which is associated with the formation of ROS
- tissue infiltration by neutrophils, their products (reactive oxygen species and enzymes)
- the release of catecholamines (adrenaline, norepinephrine) into the bloodstream, which are metabolized to ubisemiquinone with the formation of reactive oxygen species
- synthesis of nitric oxide (II) by endotheliocytes, which interacts with the superoxide anion radical to form reactogenic peroxynitrite

In addition, under conditions of ischemia, cellular antioxidant defense mechanisms are compromised (do not function at the proper level) in favor of the accumulation of free radicals.

2. Post-reperfusion damage to cells may be associated with inflammation, which develops after the restoration of blood flow in response to damaged tissue and is provided by the influx of leukocytes and plasma proteins.

3. Reperfusion damage to cells is facilitated by the activation of the complement system. Some antibodies are deposited in ischemic tissues for unknown reasons, after blood flow is restored, the complement proteins bind to them and aggravate cell damage and inflammation.

Mechanisms of cell death. Comparative characteristics of apoptosis and necrosis. Examples of intensification and insufficiency of apoptosis in pathology

There are two main forms of cell death:

1. Necrosis - from lethal damage
2. Apoptosis - from the launch of a special program

Fig. 4.2 illustrates the structural changes in cell injury resulting in necrosis or apoptosis.

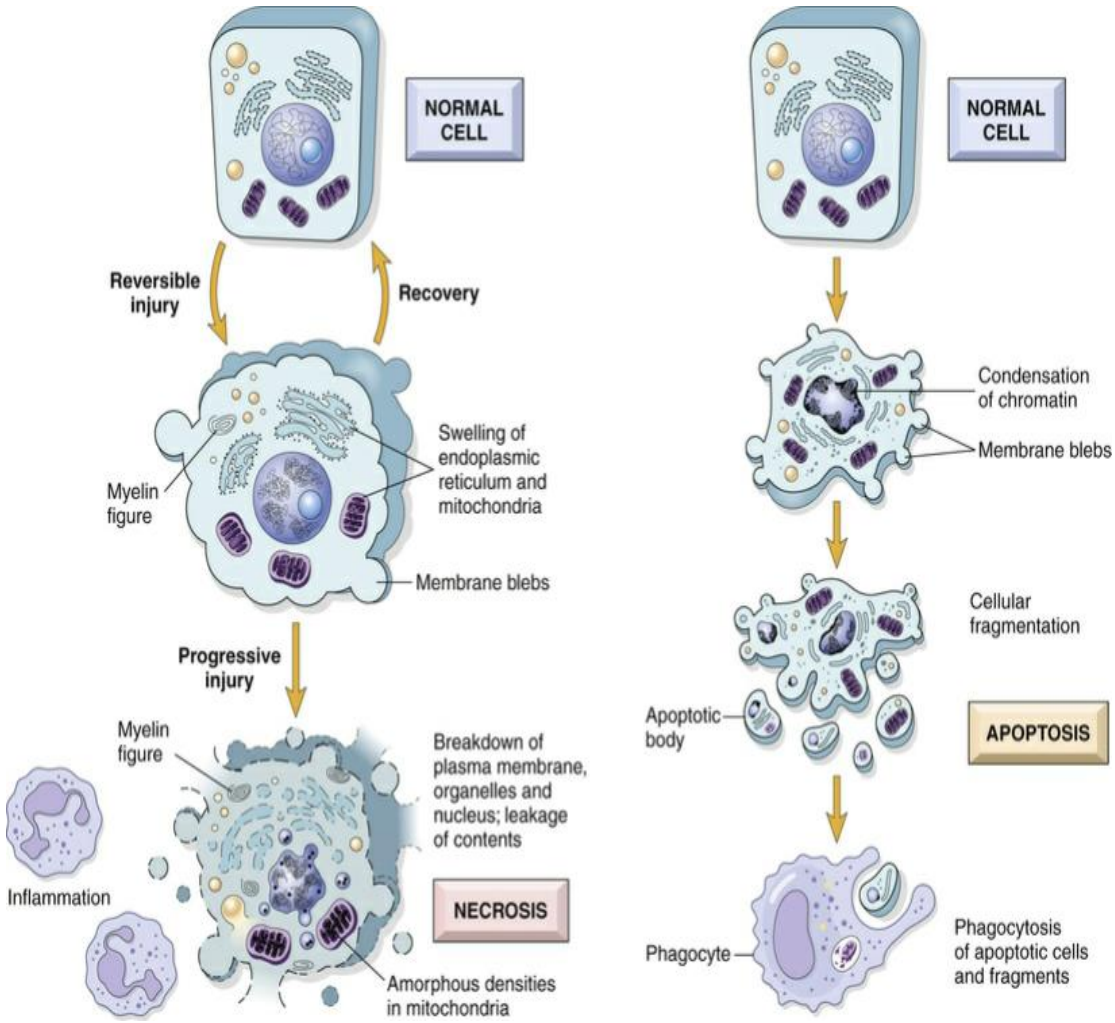

Figure 4.2 Schematic Illustration of the Morphologic Changes in Cell Injury Culminating in Necrosis or Apoptosis. Myelin figures come from degenerating cellular membranes and are noted within the cytoplasm or extracellularly. (From Kumar V et al: Cellular responses to stress and toxic insults: adaptation, injury, and death. In Kumar V, Abbas A, Aster J: Robbins & Cotran pathologic basis of disease, ed 9, St Louis, 2015, Saunders.)

Necrosis (from the Greek μεκρός - dead) described by R. Virkhov in 1859. Usually affects many cells with the formation of a necrotic zone. Necrosis - uncontrollable pathological form of cell death, developing in response to irreversible damage, characterized by the activation of hydrolytic enzymes and denaturation of intracellular proteins (autolysis).

Stages (conditionally):

1. Paranecrosis (reversible changes in structure and function)
2. Necrobiosis (changes preceding cell death)
3. Necrosis itself:

- autolysis - destruction of cells under the influence of their own hydrolytic enzymes
- heterolysis - destruction of cells under the influence of enzymes from other cells (for example, phagocytes)

Types of necrosis

- coagulation - most often (myocardial infarction)
- colliquation (abscess, cerebral infarction)
- caseous (tuberculous granuloma)
- adipose (pancreatic fiber in o. pancreatitis)
- fibrinous (vessels with arterial hypertension)

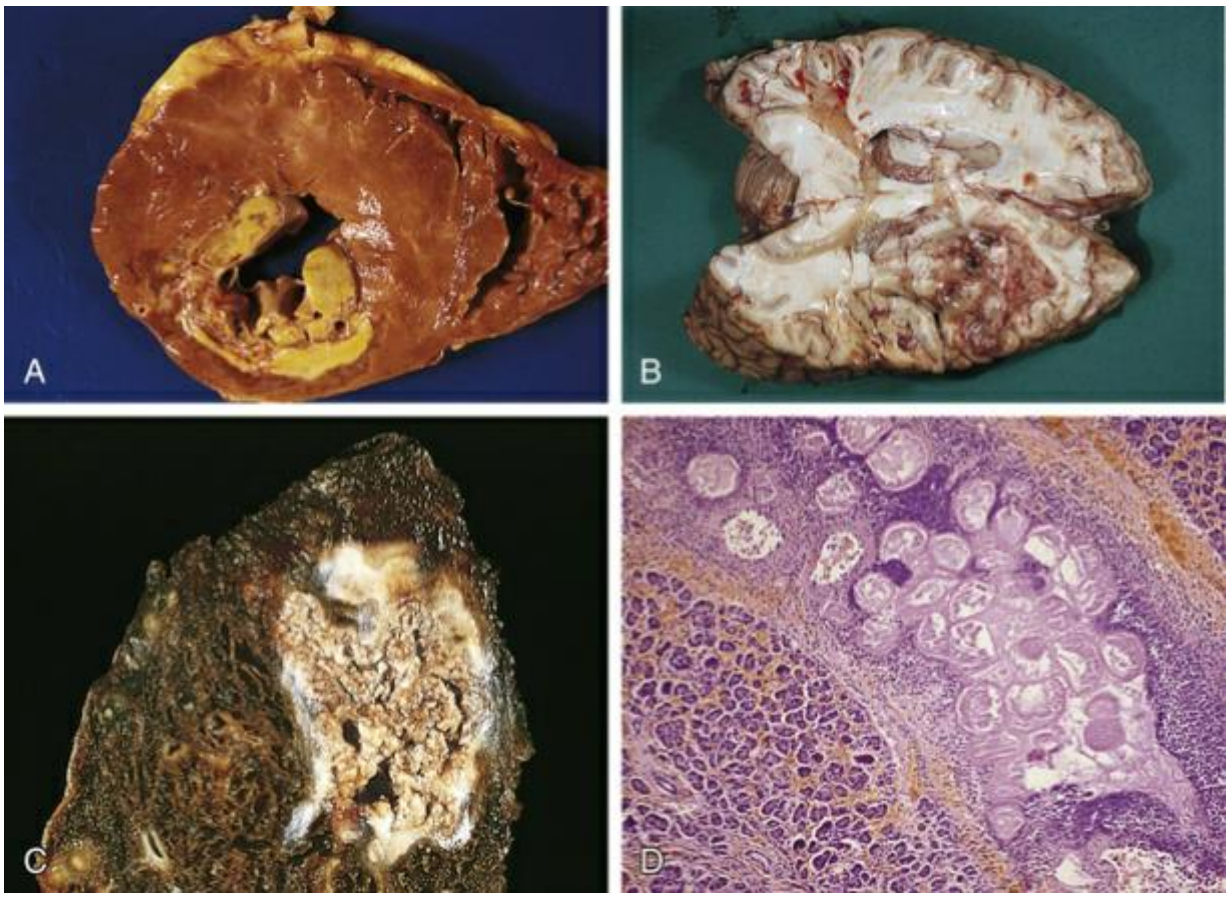

Figure 4.3 Types of Necrosis. A, Coagulative necrosis of myocardium of posterior wall of left ventricle of heart. A large anemic (white) infarct is readily apparent; note also the necrosis of papillary muscle. B, Liquefactive necrosis of the brain. The area of infarction is softened as a result of liquefactive necrosis. C, Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and cheesy debris. D, Fat necrosis of pancreas. Interlobular adipocytes are necrotic; these are surrounded by acute inflammatory cells. (A and D from Damjanov I, Linder J, editors: Anderson's pathology, ed 10, St Louis, 1996, Mosby. B from Damjanov I: Pathology for the health professions, ed 5, St Louis, 2016

Outcomes of necrosis:

- restitution - complete restoration of dead cells due to regeneration (liver)
- substitution - restoration by replacing with connective tissue (scar after myocardial infarction)
- calcification - impregnation of necrotic masses with Ca^{++}
- resorption of necrotic masses by macrophages with the formation of a cavity - pseudocysts (after a cerebral infarction)

Apoptosis (Greek απόπτωσις - leaf fall, the term was introduced by Galen, fixed by N. Walker, 1968) - a form of cell death, triggered by a special program under the influence of extracellular and intracellular factors in physiological and pathological conditions, characterized by the activation of certain genes and enzymes, which leads to the destruction of proteins and nucleic acids of the cell.

The physiological role of apoptosis is reduced to maintaining a balance between proliferation and cell death (at the stage of embryogenesis, hormone-dependent involution of the endometrium, recovery of the mammary gland after cessation of lactation, removal of aging and actively proliferating cells, clonal selection of immune cells). In pathological situations, apoptosis ensures the elimination of tumor cells, cells infected with viruses, damaged cells, pathological organ atrophy, and cell death during transplant rejection.

Apoptosis stages

1. Initiation (action of trigger factors)

- negative signal - a decrease in the effect of growth factors (for example, testosterone on the prostate after castration)
- positive signal - for example, the effects of tumor necrosis factor-alpha
- intracellular signals: an increase in the intracellular concentration of H^+, reactive oxygen species, an increase in temperature, irreversible deoxyribonucleic acid damage

2. Programming (turning on the program)

activation of enzymes of apoptosis in 2 ways:

- direct (in non-nuclear cells, for example, erythrocytes)

bypassing the genome, special proteins are activated – caspases:

● adapter proteins (caspase-8 → activation of caspase-3)

● cytochrome c (cytochrome c + Apoptotic protease activating factor 1+ caspase-9 → activation of caspase-3)

● granzymes (found in cytotoxic T-lymphocytes)

- mediated (through the genome):

● increased expression of genes - promoters of apoptosis: B-cell lymphoma 2-associated death promoter protein, B-cell lymphoma 2-associated X protein, p53

● decreased expression of genes - inhibitors of apoptosis: B-cell lymphoma 2, B-cell lymphoma-extra large

3. Implementation of the program

action of special enzymes of the suicidal biochemical pathway - effector proteases:

- caspases → destruction of cell proteins
- endonucleases → deoxyribonucleic acid and ribonucleic acid decay

→ formation of cell fragments (apoptotic bodies)

3. Removal of apoptotic bodies by phagocytosis by macrophages or nearby cells

The role of apoptosis in the pathogenesis of certain diseases

Diseases associated with inhibition of apoptosis:

1. Malignant tumors
2. Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis)
3. Viral infections (herpes, adenoviruses)
4. Diseases occurring with hypereosinophilic syndrome
5. Neuroproliferative diseases (schizophrenia)

Diseases associated with increased apoptosis:

1. Human immunodeficiency virus infection (acquired immunodeficiency syndrome)
2. Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea)
3. Diseases of the blood (myelodysplastic syndrome, hypoplastic anemia)
4. Ischemic injury (myocardial infarction, stroke, reperfusion injury)
5. Toxic liver damage
6. Kidney disease

Features of necrosis and apoptosis:

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma Membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent Inflammation	Frequent	No
Physiologic pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially deoxyribonucleic acid damage

Practical lesson 5. Inflammation. Etiology, the main pathogenesis components of the inflammatory process.

Key questions of the lesson

1. Inflammation: the term, definition, etiology, local and systemic signs of inflammation, their pathogenesis.
2. Primary and secondary alterations, changes in the microcirculatory bed vessels in inflammation, pathogenesis, manifestations.
3. Edema pathogenesis in inflammation. The biologically active substances role in the regulation of vascular wall permeability. Types of exudates, examples.
4. Edema pathogenesis in inflammation. Metabolic disorders in the inflammation focus.
5. Inflammatory mediators, classification, their sources and role in the inflammation.
6. Leukocyte reactions in inflammation: mechanisms of chemotaxis, adhesion, and emigration.

Inflammation: the term, definition, etiology, local and systemic signs of inflammation, their pathogenesis.

Inflammation is a typical pathological process that develops in response to damage, characterized by a complex of complicated, step-by-step changes in the blood, connective tissue and microcirculatory bed, aimed at removing (isolating) the damaging factor and restoring (replacing) the damaged tissues.

Etiology of inflammation

The etiological factor of inflammation is phlogogen. By nature, phlogogenic factors are divided into several groups:

1. Physical: mechanical injury, high or low temperature, ionizing radiation.
2. Chemical: acids, alkalis, free radicals.
3. Biological: exogenous (bacteria, viruses, protozoa, etc.), endogenous (factors of autoimmune aggression, autoantibodies).

There are septic inflammation, in which the phlogogen is a factor of an infectious nature, and aseptic inflammation caused by a factor of a non-infectious nature (an example of aseptic inflammation is a myocardial infarction).

Inflammatory mediators, classification, their sources and role in the inflammation (Figure 5.1**).**

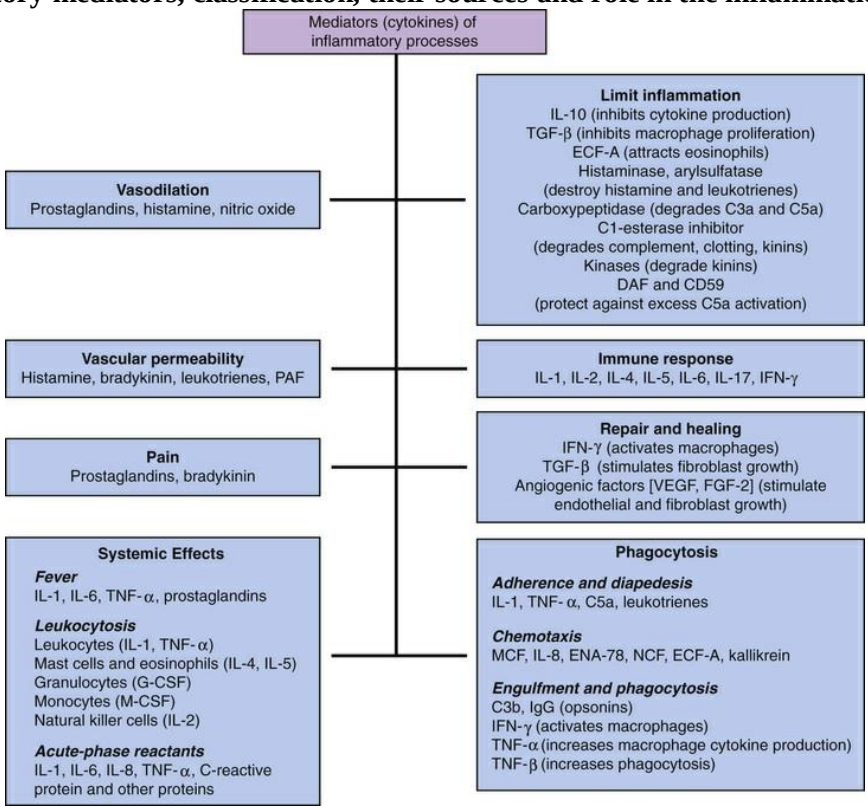

Figure 5.1 Principal Mediators of Inflammation. C3b, Large fragment produced from complement component C3; C5a, small fragment produced from complement component C5; ECF-A, eosinophil chemotactic factor of anaphylaxis; ENA, epithelial-dermoid neutrophil attractant; FGF, fibroblast growth factor; G-CSF, granulocyte

colony–stimulating factor; IFN, interferon; IgG, immunoglobulin G (predominant class of antibody in the blood); IL, interleukin; MCF, monocyte chemotactic factor; M-CSF, monocyte colony–stimulating factor; NCF, neutrophil chemotactic factor; PAF, platelet-activating factor; TGF, T-cell growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

Table 5.1 Classification of cellular inflammatory mediators

Mediators	Origin	Effects
Biogenic amines		
Histamine	Basophils, mast cells	It acts indirectly through the histamine receptors on the cell membrane. In low concentrations, histamine activates H_1-receptors, and in high concentrations H_2-receptors. Increases the venules permeability, expands arterioles, activates the white blood cells migration to the focus of inflammation, participates in the formation of pain and itching feelings.
Serotonin	Platelets, mast cells	Causes first narrowing, and then expansion of microvessels. Increases the vascular wall permeability, participates in the formation of a pain sense.
Adrenaline and noradrenaline	Nerve endings in the focus of inflammation, platelets	They bind to the α-adrenoreceptors of smooth muscle arterioles cells and increase their tone.
Cytokines		
Interleukins (IL-1, IL-6, IL-8, etc.)	Monocytes, macrophages, lymphocytes, endotheliocytes	White blood cells activation and chemotaxis, activation of phagocytosis, proliferation and differentiation stimulation of various cells, are involved in the fever formation.
Interferon-γ	Monocytes, macrophages	Stimulate phagocytosis, white blood cells cytotoxic activity. Antiviral action, are involved in the fever formation.
Phospholipid products		
Prostaglandins, thromboxanes	Platelets, endothelial cells, mast cells. Prostaglandins are formed from cell membranes phospholipids under the enzyme phospholipase A_2 action. As a result of the phospholipids cleavage formed arachidonic acid, from which, with the participation of the enzyme cyclooxygenase, rostaglandins are formed	Prostaglandin I_2 causes vasodilation, inhibits platelet aggregation. Thromboxane A_2 causes vasoconstriction, increases platelet aggregation. Prostaglandins D_2, E_2 cause vasodilation and increased vascular wall permeability.
Leukotrienes (C_4, D_4, E_4)	White blood cells, mast cells. They are formed when the lipoxygenase pathway of arachidonic acid metabolism is activated	Vascular spasm of the microcirculatory bed, increased vascular wall permeability, chemoattraction factors for phagocytes
Nitric oxide, reactive oxygen species (H_2O_2, $O^{\cdot}_2$, $\cdot OH^-$)	Endothelial cells, macrophages	Regulation of vascular wall tone, bactericidal effect

Plasma inflammatory mediators are formed in the liver, are transported in the blood plasma in an inactive form and are activated in the inflammation focus. Plasma inflammatory mediators include:

1. Components of the kinin system (bradykinin);
2. Components of the complement system (C3a, C5a);
3. Components of the fibrinolysis and fibrin formation system (Table 5.2).

Table 5.2 Classification of plasma inflammatory mediators

Mediators	Origin	Effects
Components of the kinin system (kallikrein, bradykinin)	Hepatocytes	Increased vessels walls permeability of the microcirculatory bed (10 times more active than histamine), dilation of the arterioles lumen, stimulation of phagocyte migration, the formation of a pain sense
Components of the complement system (complement system proteins)	Hepatocytes	Chemotaxis and phagocytosis activation, cytolytic and bactericidal effects
Components of the fibrinolysis and fibrin formation system (thrombin, fibrin, plasmin, etc.)	Hepatocytes	Regulation of the thrombosis and fibrinolysis mechanisms

Acute inflammation pathogenesis

In the inflammatory process pathogenesis are distinguished the following key events (Figure 5.2):

1. Alteration stage:
1) primary alterations
2) secondary alterations
2. Vascular-exudative stage:
1) vascular reactions
2) exudation
3) leukocyte reactions
3. Proliferation stage:
1) termination of alterative and vascular – exudative reactions
2) connective tissue synthesis and angiogenesis

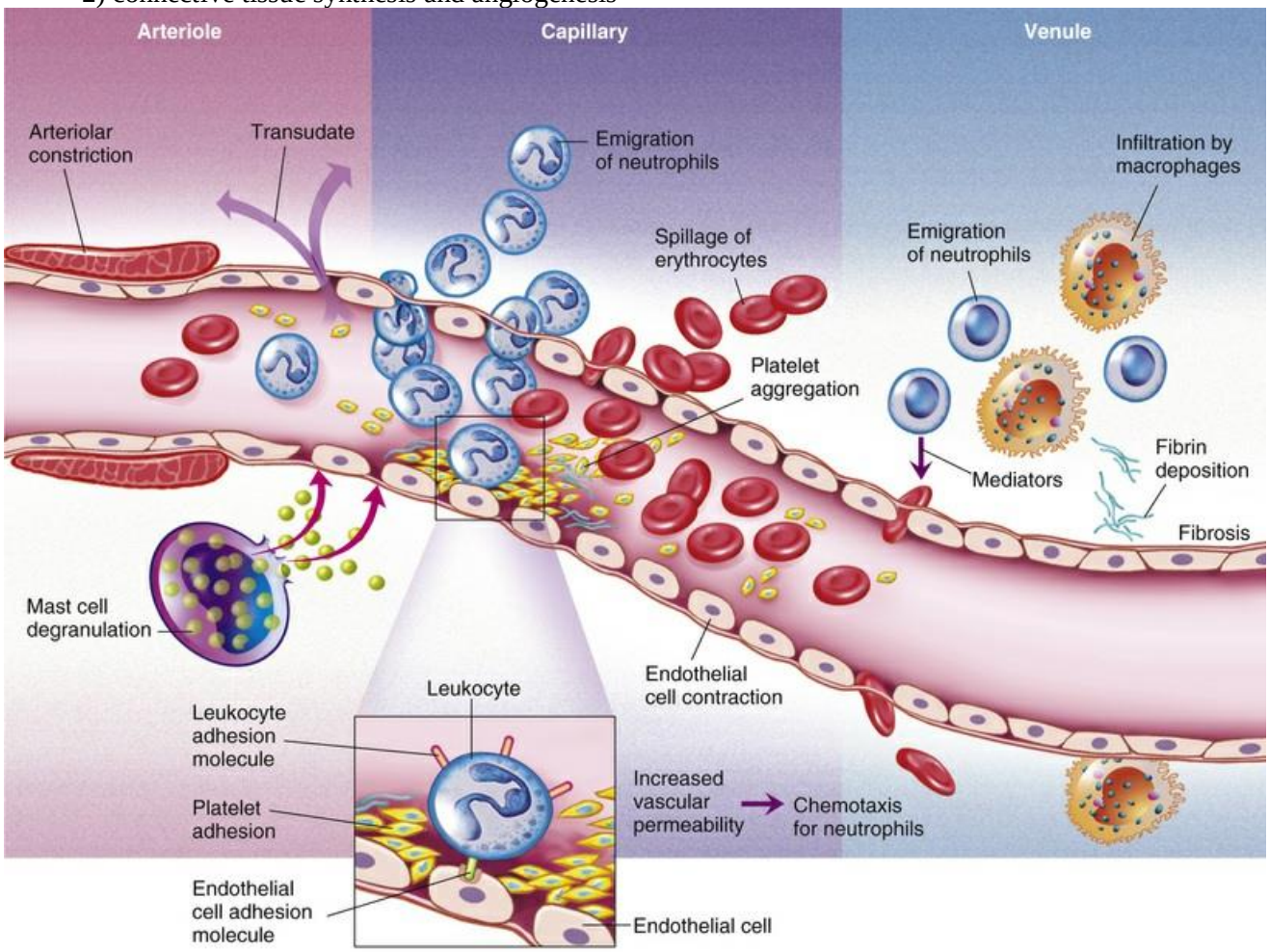

Figure 5.2 Sequence of events in the acute inflammatory response.

Primary and secondary alterations, changes in the microcirculatory bed vessels in inflammation, pathogenesis, manifestations.

Alterations (from Lat. alteratio-change) – is a change of the cell structure, cell metabolism, physical and chemical tissue properties and the biologically active substances concentration in the inflammation focus.

There are primary and secondary alterations.

Primary alteration is a complex of changes in the inflammation focus caused by a phlogogenic factor. In the process of primary alteration, direct damage to cell structures and tissue occurs, destruction of cell membranes, release of lysosomal enzymes into the intercellular space, displacement of the physical and chemical tissue constants (pH, osmotic pressure, etc.). Primary alteration is formed immediately after the action of the phlogogenic factor and is characterized mainly by cell integrity irreversible violations, necrosis.

Secondary alteration is tissue damage in the inflammation focus, which is caused by the primary alteration products, as well as cellular and humoral inflammatory process participants. During secondary alterations, the damage zone expands.

Edema pathogenesis in inflammation. The biologically active substances role in the regulation of vascular wall permeability. Types of exudates, examples.

Vascular-exudative stage

Vascular reactions consistently include the following events:

1. Short-term spasm of the arterioles
2. Arterial hyperemia
3. Venous hyperemia
4. Stasis

Arterial hyperemia. The leading development mechanism is myoparalytic. As a result of the action of inflammatory mediators (bradykinin, histamine, nitric oxide II) on the smooth muscle cells of the arterioles, their relaxation occurs, the vessel lumen expands and the blood flow to the inflammation focus increases. With the blood flow oxygen, nutrients, white blood cells and inflammatory mediators enter the inflammation focus. Arterial hyperemia is manifested by **redness** (rubor) of the inflammation focus.

Venous hyperemia and stasis. They develop under the influence of a complex of factors:

1. Intravascular factors:
   - marginal standing of white blood cells
   - platelet adhesion and aggregation
   - red blood cell sludge
   - fibrin formation in the vessel lumen
   - swelling of endotheliocytes
2. Extravascular factors:
   - compression of venules with exudate

In the venous hyperemia stage, the blood flow in the inflammation focus slows down and the blood liquid part and the shaped elements begin to exit into the tissues. Venous hyperemia is manifested by tissue and inflammation focus **edema** (tumor), **pain** (dolor) and local **hyperthermia** (calor).

Exudation is the process of releasing the blood liquid part and shaped elements into the inflammation focus.

Exudate is a fluid that accumulates in the body tissues or cavities during inflammation.

Exudation mechanisms

1. An increase in the microvessels walls permeability (membranogenic factor) is a leading factor in the development of edema in inflammation.

2. The difference between osmotic and oncotic pressure between blood plasma and fluid in the inflammation focus (osmotic and oncotic factors).

3. Increased hydrostatic pressure in the blood vessel (hemodynamic factor).

Microvessels walls permeability increase occurs with the participation of inflammatory mediators. Inflammatory mediators (histamine, bradykinin) act on endothelial cells, promote their reduction and the formation of interendothelial gaps, through which plasma and blood cells enter the inflammation focus. White blood cells secrete enzymes (elastase, collagenase), which break down the vessel basal membrane, facilitate exudation.

The difference between oncotic and osmotic pressure is provided by the accumulation of osmotically active products and proteins from destroyed cells in the inflammatory focus, as well as proteins that exit the blood plasma into the inflammatory focus. Thus, the oncotic and osmotic pressure in the inflammation focus increases, which facilitates the exudation process.

A hydrostatic pressure increase in the vessel occurs due to an increase in blood flow to the stage of arterial hyperemia and a violation of blood outflow to the stage of venous hyperemia. A hydrostatic pressure increase in the vessel contributes to the fluid filtration through the vessel wall into the inflammation focus.

Depending on the composition, the following exudate types are distinguished:

1. Serous exudate-contains 3-5% protein, single polymorphonuclear leukocytes, single cells. Examples of diseases: serous peritonitis, pleurisy, burns.

2. Hemorrhagic exudate-contains 4-6% protein, red blood cells. Examples of diseases: anthrax, flu.

3. Purulent exudate-contains 6-8% protein, polymorphonuclear leukocytes, microorganisms (staphylococci), cells of damaged tissue. Examples of diseases: abscess, phlegmon.

4. Putrefactive exudate-contains 6-8% protein, polymorphonuclear leukocytes, putrefactive bacteria (anaerobic), cells of damaged tissue. Examples of diseases: gas gangrene.

5. Fibrinous exudate-contains fibrinogen and fibrin. Examples of diseases: dysentery, tuberculosis, diphtheria.

Leukocyte reactions in inflammation: mechanisms of chemotaxis, adhesion, and emigration.

In the exudation stage, there is a gradual white blood cells exit into the inflammation focus. The following leukocyte reactions stages are distinguished:

1. Chemotaxis (migration) of white blood cells
2. Adhesion and activation of white blood cells
3. Emigration of white blood cells
4. Phagocytosis

Chemotaxis is the directed white blood cells movement along the chemoattractants concentration gradient.

Chemoattractants include microorganisms' components, leukotriene B4, IL-8, complement system proteins (C3a, C5a), and many others. Moving towards the chemoattraction factors, white blood cells exit the axial cylinder of the blood flow and approach the vascular bed wall. This is also facilitated by the slowing down of the blood flow to the venous hyperemia stage. Gradually, the movement speed of white blood cells slows down, and they line up along the vascular wall (marginal standing of white blood cells).

The next stage of leukocyte reactions is the white blood cells adhesion to the vascular wall. It is carried out in two stages. The first stage is selectin-dependent-reversible or "soft" adhesion. It is carried out by selectins on the white blood cells (L - selectins) and endothelial cells (E - selectins and P - selectins) surface. There is a reversible attachment of the white blood cell to the vascular wall, and the cell rolls along the vascular wall. This process is called white blood cell rolling. The second stage is tight adhesion, which is provided by the adhesive molecules integrins. At the place where the concentration of chemoattractants is highest, dense adhesion molecules are expressed on endothelial cells and white blood cells. On white blood cells, it is a complex of β_2 - integrin (CD11/CD18), and on endothelial cells, VCAM, ICAM, and other molecules. As a result of tight adhesion, the leukocyte stops, attaches tightly to the vessel wall and prepares for the next stage of leukocyte reactions - emigration (extravasation or transition through the vascular wall).

White blood cells emigration. The white blood cell passage through the vascular wall is carried out due to the vascular wall permeability (interendothelial slits), as well as the release of neutrophils and monocytes of their own enzymes (collagenases, elastases) that cleave the endothelium basement membrane, which facilitates diapedesis. After leaving the vessel, the white blood cell moves towards the phagocytosis object in the inflammation focus.

Phagocytosis is the phagocytic objects absorption and digestion by phagocytes.

Stages of phagocytosis:

1. Phagocytosis object recognition and attachment of the phagocyte to it. Opsonin molecules cover the phagocytosis object and make it recognizable to the phagocyte. Opsonins include complement proteins C3b, lysozyme, C-reactive protein, and IgG.

2. Object immersion in the phagocyte and the phagosome formation.

3. Phagocytosis object destruction. It is carried out in two ways: oxygen-dependent with the reactive oxygen species participation (superoxidanion radical, hydrogen peroxide, hydroxyl radical) and oxygen-independent, which is carried out with the lysosomal enzymes (elastase, protease, lysozyme, defensins, the main main protein) help when the lysosome and phagosome merge inside the phagocyte.

4. Processing of antigens for immunocytes on the phagocyte surface by means of HLA-I, HLA-II complexes.

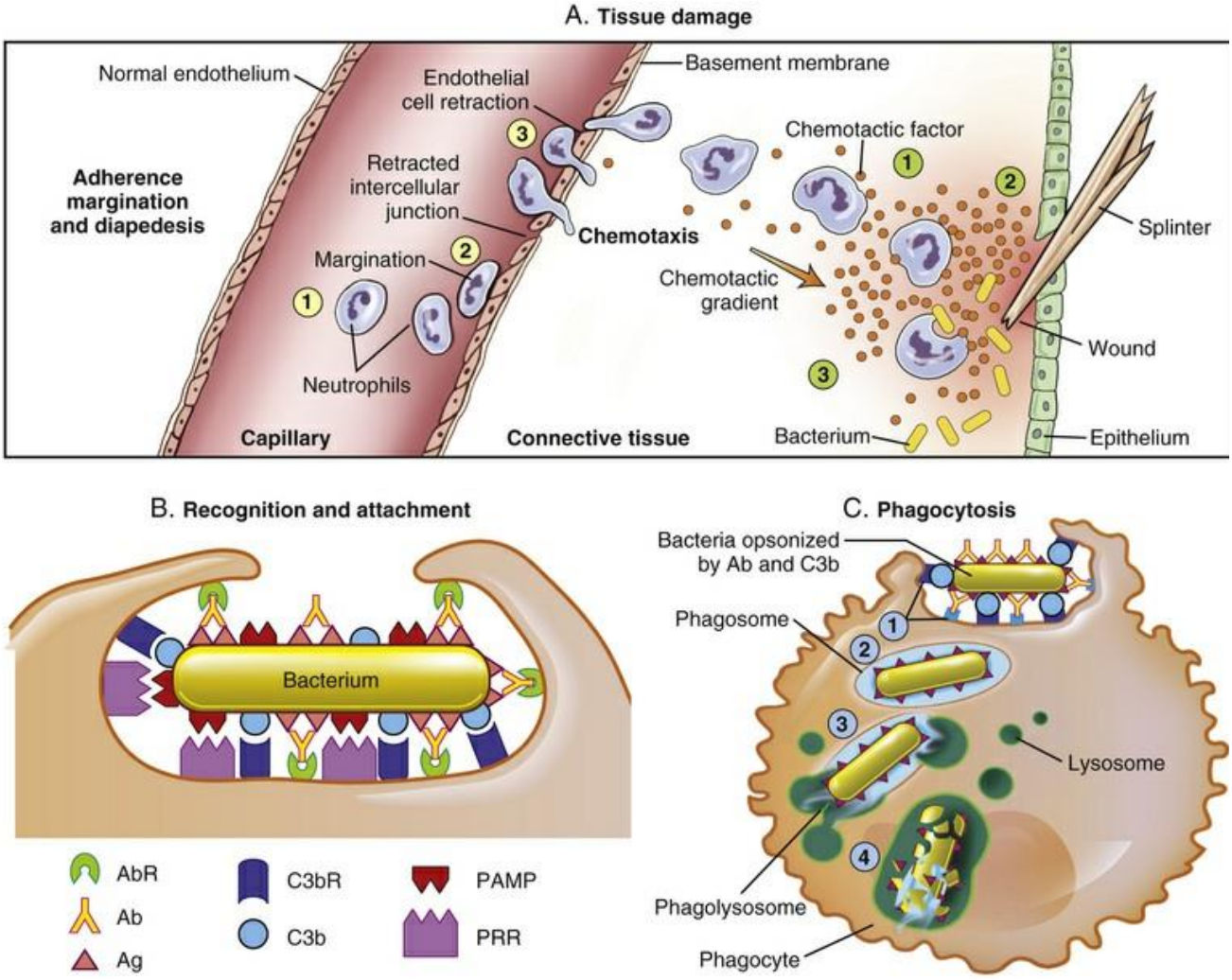

Figure 5.3 Process of Phagocytosis. The process that results in phagocytosis is characterized by three interrelated steps: adherence and diapedesis, tissue invasion by chemotaxis, and phagocytosis. A, Tissue damage. Adherence, margination, and diapedesis: The primary phagocyte in the blood is the neutrophil, which usually moves freely within the vessel (1). At sites of inflammation, the neutrophil progressively develops increased adherence to the endothelium, leading to accumulation along the vessel wall (margination or pavementing) (2). At sites of endothelial cell retraction, the neutrophil exits the blood by means of diapedesis (3). Chemotaxis: In the tissues, the neutrophil detects chemotactic factor gradients through surface receptors (1) and migrates toward higher concentrations of the factors (2). The high concentration of chemotactic factors at the site of inflammation immobilizes the neutrophil (3). B, Recognition and attachment. Specific receptors and ligands for recognition and attachment. C, Phagocytosis. (1) Opsonized microorganisms are recognized and bind to the surface of a phagocyte through specific receptors. (2) The microorganism is engulfed (ingested) into a phagocytic vacuole, or phagosome. (3) Lysosomes fuse with the phagosome, resulting in the formation of a phagolysosome. During this process the microorganism is exposed to products of the lysosomes, including a variety of enzymes and products of the hexose-monophosphate shunt (e.g., H_2O_2). (4) The microorganism is killed and digested. Ab, Antibody; AbR, antibody receptor; Ag, antigen; C3b, complement component C3b; C3bR, complement C3b receptor; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor

Stage of proliferation

There are three main events that occur during the proliferation stage:

1. Attenuation of alterative reactions as a result of:

- final removal of the phlogogenic factor by mononuclear leukocytes in the focus of inflammation (monocytes/macrophages, lymphocytes);
- inactivation of inflammatory mediators-they are destroyed by themselves, or are broken down by enzymes.

2. Formation of the intercellular matrix as a result of:

- secretion of growth factors by macrophages and other cells (epidermal growth factor, fibroblast growth factor, platelet growth factor),
- activation of fibroblasts and synthesis of intercellular matrix components
- activation of angioblasts and formation of new vessels (neoangiogenesis).

3. Repair. The lost elements are recreated after being damaged.

The reparation may be complete (restitution) or incomplete (substitution).

Complete repair occurs after the formation of connective tissue and blood vessels, as a result of the parenchymal cells division and the damaged tissue restoration, Complete repair is possible in tissues with high regenerative potential (bone marrow, epithelial tissue, liver, kidneys, endocrine glands).

Incomplete repair occurs in cells with low regenerative potential (nerve tissue, myocardium, striated muscle tissue). The damaged tissue is repaired by replacing it with connective tissue and forming a scar.

Manifestations of inflammation (Figure 5.4**)**

There are local and systemic manifestations of inflammation. Local manifestations of inflammation include: redness (rubor), pain (dolor), swelling (tumor), fever (calor), impaired function (functia laesa). Systemic manifestations of inflammation are divided into laboratory and clinical manifestations.

Laboratory signs of inflammation:

* leukocytosis (the white blood cells number increase per unit volume of blood),

* shift of the leukocyte formula to the left (increase in the content of young and rod-shaped neutrophils in the leukocyte formula),

* increased erythrocyte sedimentation rate,

* dysproteinemia (the globulins concentration increase and the albumin concentration decrease)

* increased concentration of acute phase reactants (C-reactive protein, fibrinogen, serum amyloid A) in the blood.

Systemic manifestations of inflammation include fever, weakness, fatigue, increased heart rate, increased frequency of respiratory movements, etc.

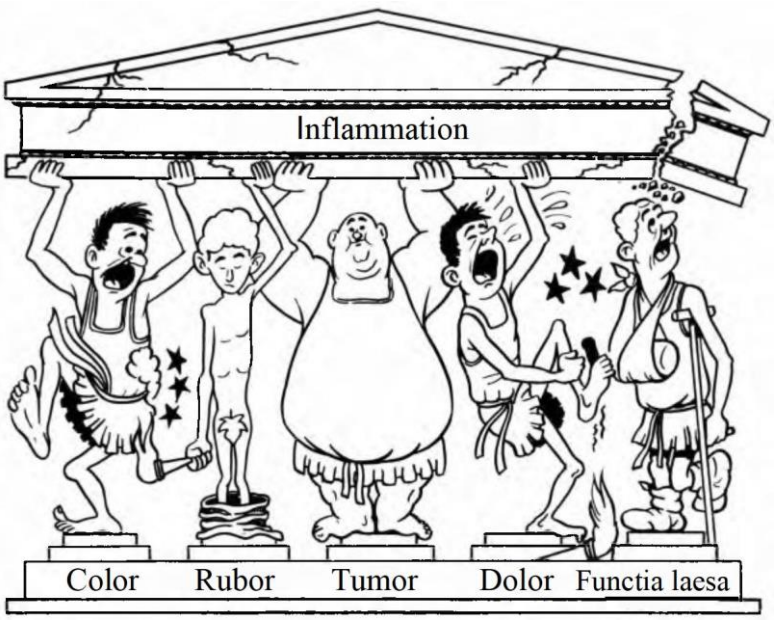

Figure 5.4 Manifestations of inflammation

Practical lesson 6. Inflammation. Acute phase response.

Key questions of the session

1. Chronic inflammation: features of etiology, pathogenesis, examples of diseases. Principles of anti-inflammatory therapy.
2. Acute phase response: definition of the concept, meaning, pathogenesis of manifestations.

Chronic inflammation: features of etiology, pathogenesis, examples of diseases. Principles of antiinflammatory therapy.

Chronic inflammation is inflammation of a long course, in which the processes of alteration, exudation and proliferation occur simultaneously. The chronic inflammation to the complications of obesity, particularly insulin resistance, type 2 diabetes mellitus, cardiovascular disease, and cancer.

Etiological factors of chronic inflammation

1. Inorganic substances (for example, silicon dioxide) that cannot be removed from the body. Long-term inhalation of particles of silicon dioxide, which do not decompose and settle on the surface of the alveoli, contributes to the development of silicosis, a chronic inflammatory lung disease.
2. Persistent infections. Microorganisms that are difficult to remove (mycobacteria, treponema pallidum, fungi) cause constant activation of leukocytes and inflammation becomes chronic.
3. Autoantibodies. The synthesis of autoantibodies for autoantigens constantly present in the body (cell receptors, components of the cell nucleus, membrane phospholipids) contributes to tissue damage and the development of chronic inflammation by an autoimmune mechanism.

Chronic inflammation is characterized by a set of tissue destruction processes as a result of the constant action of an etiological factor, infiltration of the inflammation focus by mononuclear leukocytes, as well as the repair of damaged tissue.

Chronic inflammation is characterized by a dense infiltration of lymphocytes and macrophages. If macrophages are unable to limit the tissue damage or infection, the body attempts to wall off and isolate the infected area, thus forming a granuloma. Granulomas may form if neutrophils and macrophages are unable to destroy microorganisms during the acute inflammatory response. For example, infections caused by some bacteria (Listeria sp., Brucella sp.), fungi (histoplasmosis, coccidioidomycosis), and parasites (leishmaniasis, schistosomiasis, toxoplasmosis) can result in granuloma formation. Large antigen-antibody complexes such as those present in rheumatoid arthritis also can result in the formation of these structures. TNF-α primarily drives granuloma formation. Some macrophages differentiate into large epithelioid cells, cells that are incapable of phagocytosing large bacteria but are capable of taking up debris and other small particles. Other macrophages fuse into multinucleated giant cells, which are active phagocytes that can engulf very large particles—larger than those that can be engulfed by a single macrophage. These two types of specialized cells form the center of the granuloma, which is surrounded by a wall of lymphocytes. The granuloma itself is also often encapsulated by fibrous deposits of collagen and may become cartilaginous or possibly calcified by deposits of calcium carbonate and calcium phosphate.

Other types of cells are also involved in the pathogenesis of chronic inflammation: plasma cells, eosinophils, mast cells. Activated macrophages present antigens to T-lymphocytes, and also release cytokines (TNF-alpha, IL-12) that activate T-lymphocytes. In turn, activated T cells, producing cytokines (IFN-γ, IL-4, etc.) attract monocytes from the bloodstream to the inflammation focus and promote their activation. As a result of these interactions between macrophages and T-lymphocytes, a chronic response to injury develops.

Plasma cells synthesize antibodies (IgG, IgM) against persistent foreign or self antigens, ensuring the participation of humoral factors in the chronicity of inflammation. Eosinophils and mast cells are involved in IgE-mediated reactions. Mediators of eosinophils (the main basic protein, histaminase) or mast cells (histamine) are involved in both enhancing and limiting the inflammatory process.

Acute phase response: definition of the concept, meaning, pathogenesis of manifestations

The acute phase response is a complex of systemic reactions of the body triggered by tissue damage and the release of mediators into the bloodstream (IL-1, IL-6, IL-8, TNF-α, IFN-γ, and others) (Table 6.1).

Table 6.1 Cytokines in inflammation

Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
tumor necrosis factor	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules

		and secretion of other cytokines; systemic effects
interleukin-1	Macrophages, endothelial cells, some epithelial cells	Similar to tumor necrosis factor; greater role in fever
interleukin-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
interleukin-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
interleukin-12	Dendritic cells, macrophages	Increased production of Interferon-γ
Interferon-γ	T lymphocytes, natural killer cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
interleukin-17	T lymphocytes	Recruitment of neutrophils and monocytes

The “acute phase response” is a reaction that occurs when pyrogenic and other cytokines are released in response to infection and inflammation. In addition to fever, other symptoms occur including anorexia, fatigue, malaise, somnolence, and loss of concentration (Table 6.2).

Table 6.2 Role of mediators in different reactions of inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C4, D4, E4
Chemotaxis, leukocyte recruitment and activation	tumor necrosis factor, interleukin-1 Chemokines C3a, C5a Leukotriene B4
Fever	interleukin-1, tumor necrosis factor Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

At the cellular level, inflammatory pyrogenic cytokines promote muscle catabolism and hyperglycemia (gluconeogenesis, glycogenolysis, and insulin resistance) by stimulating release of adrenocorticotropic hormone and glucocorticoids to support glucose-consuming cells (Figure 6.1).

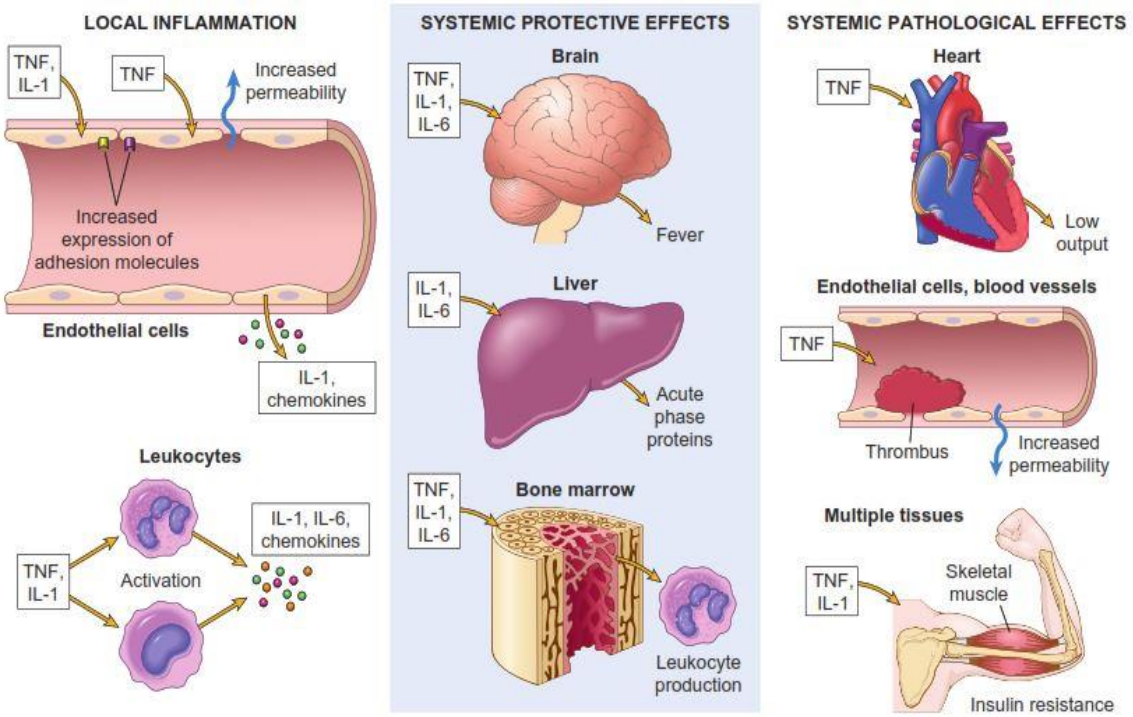

Figure 6.1 Major roles of cytokines in acute inflammation. PDGF - Platelet-derived growth factor; PGE - prostaglandin E; PGI - prostaglandin I

The emerging response of the acute phase contributes to the mobilization of the body's defenses aimed at limiting the action, removing the damaging factor, rapid and coordinated restructuring of metabolism to maintain homeostasis, and limiting the scale of alteration.

The acute phase response is characterized by a change in the serum levels of proteins (mediators) of the acute phase response.

Acute phase proteins, the number of which increases during the acute phase reaction, are called **positive**: C-reactive protein, serum amyloid A, fibrinogen, haptoglobin, α1-antitrypsin, α1-antichymotrypsin, ceruloplasmin, C3-component of complement, inactivator of C1-component of complement, fibronectin and others.

Proteins of the acute phase, the concentration of which decreases in the blood plasma during the reaction of the acute phase, are called **negative**: transferrin, albumin, transthyretin, α2 - glycoprotein.

The severity of the acute phase response is determined by the concentration of acute phase response mediators in the blood. The scheme of acute phase response is represented on Fig. 6.2

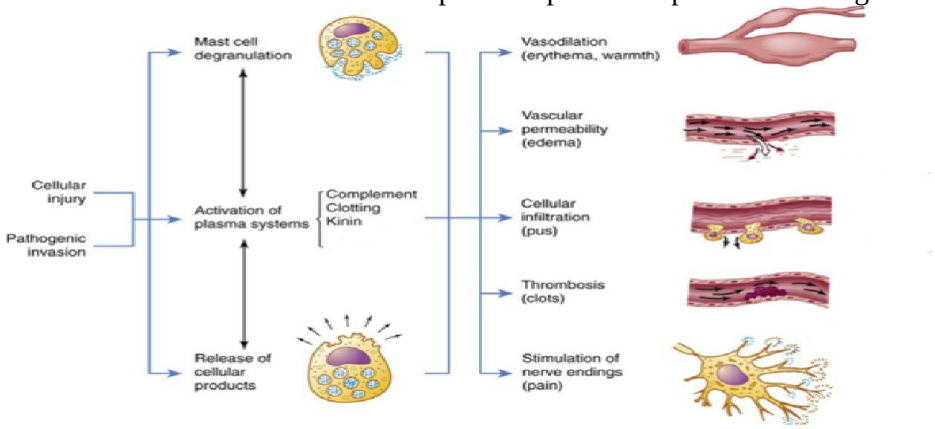

Figure 6.2 Acute Inflammatory Response. Inflammation is usually initiated by cellular injury, which results in mast cell degranulation, the activation of three plasma systems, and the release of subcellular components from the damaged cells. These systems are interdependent, so that induction of one (e.g., mast cell degranulation) can result in activation of the other two. The result is the development of microscopic changes in

the inflamed site, as well as characteristic clinical manifestations. The figure numbers refer to those in which more detailed information may be found on that portion of the response.

Although, as might be expected, many variables may modify the basic process of inflammation, including the nature and intensity of the injury, the site and tissue affected, and the responsiveness of the host, all acute inflammatory reactions typically have one of three out-comes (Fig. 6.3):

1. Complete resolution. In a perfect world, all inflammatory reactions, once they have succeeded in eliminating the offending agent, should end with restoration of the site of acute inflammation to normal. This is called resolution and is the usual outcome when the injury is limited or short-lived or when there has been little tissue destruction and the damaged parenchymal cells can regenerate. Resolution involves removal of cellular debris and microbes by macrophages, and resorption of edema fluid by lymphatics.

2. Healing by connective tissue replacement (scarring, or fibrosis). This occurs after substantial tissue destruction, when the inflammatory injury involves tissues that are incapable of regeneration, or when there is abundant fibrin exudation in tissue or in serous cavities (pleura, peritoneum) that cannot be adequately cleared. In all these situations, connective tissue grows into the area of damage or exudate, converting it into a mass of fibrous tissue, a process also called organization.

3. Progression of the response to chronic inflammation (discussed later). Acute to chronic transition occurs when the acute inflammatory response cannot be resolved, as a result of either the persistence of the injurious agent or some interference with the normal process of healing.

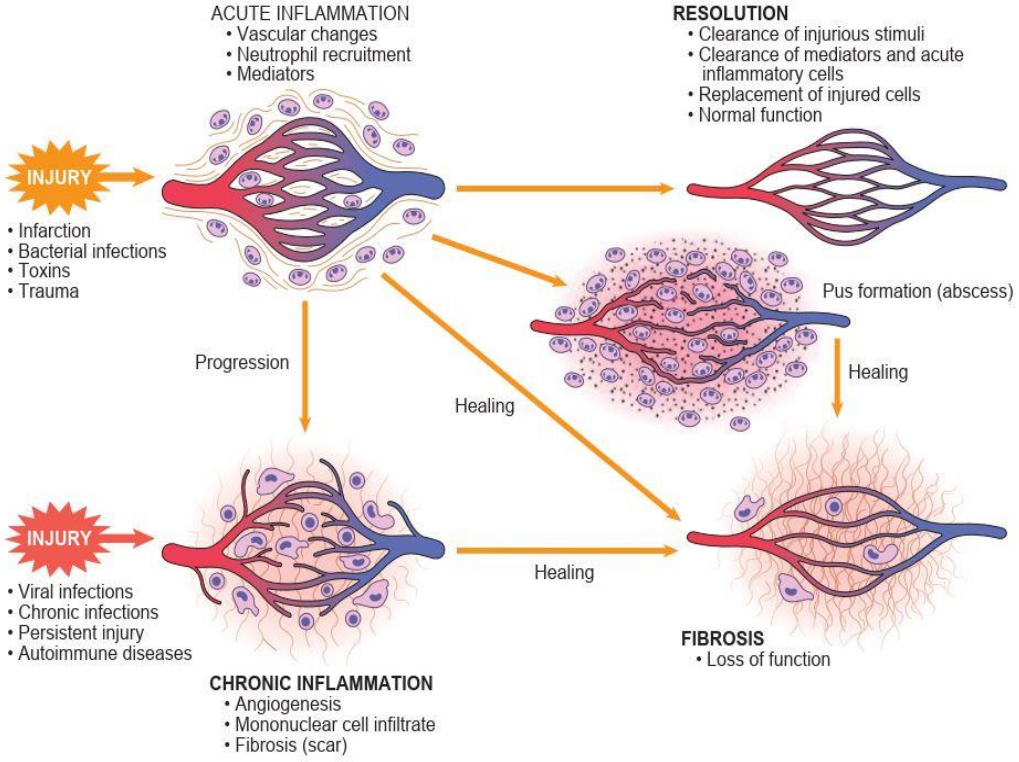

Figure 6.3 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

Practical lesson 7. Pathophysiology of the immune system. Allergy. Classification of allergy

Key questions of the lesson

1. Allergy: concept definition, classification of allergic reactions according to Jell and Coombs.
2. Allergens: concept definition, classification. Routes of entry into the body. The concept of sensitization and desensitization.
3. General pathogenesis of allergic reactions. Stages of allergic reactions.
4. Allergic reactions of type I (anaphylactic). Examples. Etiology, pathogenesis, principles of prevention and treatment.
5. Allergic reactions of type II (cytotoxic). Examples. Etiology, pathogenesis, principles of prevention and treatment.
6. Allergic reactions of type III (immunocomplex). Examples. Etiology, pathogenesis, principles of prevention and treatment. Serum sickness.
7. Allergic reactions of type IV (cell-mediated). Examples. Etiology, pathogenesis, principles of prevention and treatment.

Allergy: concept definition, classification of allergic reactions according to Jell and Coombs.

Allergy (allos-other, ergos-action), an allergic reaction is an increased body sensitivity to substances of a protein and non-protein nature (allergens), leading to damage to cells and tissues, which is based on immunological mechanisms.

Classification of allergic reactions

Depending on the development rate and the mechanisms of the immune response, there are immediate hypersensitivity reactions (IHS), with a predominantly humoral mechanism of development, and delayed hypersensitivity reactions (DHS) with a predominantly cellular mechanism of development.

IHS reactions occur a few minutes (20-30 minutes) after repeated contact with the allergen, are realized due to the action of ready-made antibodies of various specificity and lymphocytes.

DHS reactions occur several hours or days (48-72 hours) after repeated contact with the allergen. They are realized due to the allergen interaction with T-lymphocytes, develop by the mechanism of chronic inflammation with the mononuclear cells participation: monocytes/macrophages, lymphocytes.

Currently, the classification of immunopathological reactions, which was proposed by P. Gell and R. Coombs in 1969, is used. According to this classification, there are four main types of hypersensitivity reactions (later a fifth type of reaction was proposed – anti-receptor). The main types of allergic reactions and their brief characteristics are presented in Table 7.1.

Table 7.1 Classification of immunopathological reactions by P. Gell and R.Coombs

Type of hypersensitivity reaction	Allergen	Mechanism of development	Examples of diseases
Type I (IgE-mediated) (atopic, anaphylactic, reaginic)	Soluble, exogenous.	Immediate release of vasoactive and spasmogenic substances from mast cells after interaction with IgE antibodies on their surface.	Atopic bronchial asthma, pollinosis, allergic rhinitis, allergic conjunctivitis, urticaria, Quincke's edema, anaphylactic shock.
Type II (tissue-specific) (it is caused by cytotoxic reactions mediated by antibodies)	Components of the cell membrane or substances sorbed on the cell surface.	Cytotoxic reactions mediated by the interaction of complement proteins or cytotoxic lymphocytes with IgG, IgM antibodies on the surface of target cells.	Hemolytic anemia, Goodpasture's syndrome, thrombocytopenic purpura, Rh conflict, agranulocytosis.
Type III (immune complex–mediated)	Soluble, circulates in the bloodstream (foreign protein, nuclear antigens).	The formation of immune complexes of antigen-antibody (IgG, IgM) and their deposition on the vascular wall, which is accompanied by the activation of complement,	Serum sickness, systemic lupus erythematosus, Arthus phenomenon, allergic alveolitis

		the development of inflammation and tissue damage.	
Type IV (cell-mediated)	Soluble, presented by antigen-presenting cells.	Tissue damage is mediated by sensitized lymphocytes.	Tuberculosis, leprosy, contact dermatitis, schistosomiasis, celiac disease.
Type V (anti-receptor)	A receptor on the cell surface (receptors for acetylcholine, thyroid-stimulating hormone).	Blocking or stimulating the action of IgG, IgM antibodies after binding to the cell receptor.	Myasthenia gravis, Graves' disease

Allergens: concept definition, classification. Routes of entry into the body.

The allergy etiological factor is an allergen. These are substances (lipopolysaccharides, proteins, glycoproteins, etc.) that, when ingested, can cause an allergic reaction.

Classification of allergens:

1. On the way to the body: inhaled (pollen of plants, herbs, trees, dust components), parenteral (antibiotics, serums, anesthetics), contact (cosmetics and detergents, dyes), enteral (animal and plant food), transplantental.

2. By distribution in the environment: aeroallergens, household, industrial, sensitizers.

3. By origin: infectious, household, tissue, epidermal, insect, pollen, fungal.

General pathogenesis of allergic reactions. Stages of allergic reactions.

In the pathogenesis of allergic reactions, it is customary to distinguish three stages:

1. The immunological stage is a immune reactions set that develop after the allergen enters the body. With the development of reactions of the type of IHS in this stage, the formation of antibodies – immunoglobulins, with reactions of the type of DHS the allergen interacts with the T-lymphocyte.

2. Pathochemical stage – the stage of release, synthesis or activation of biologically active substances-allergy mediators.

3. Pathophysiological stage – a clinical manifestations set as a result of the allergy mediators action.

Allergic reactions of type I (anaphylactic). Examples. Pathogenesis.

Type I allergic reactions follow the mechanism of hyperergic inflammation and are associated with IgE - mediated mast cell degranulation.

The immunological stage (Figure 7.1 A**)** proceeds in several stages.

1. Recognition. It occurs at the initial contact with the allergen, which most often penetrates through the skin or mucous membranes, is absorbed by the antigen-presenting cell and presented to naive T-cells.

2. Activation of B-lymphocytes occurs after naive T-cells differentiate into Th2-lymphocytes, secrete cytokines IL-4, IL-5, IL-13 which activate B-lymphocytes.

3. Activated B-lymphocytes differentiate into plasma cells and produce IgE antibodies. A special feature of these antibodies is the presence of the Fc fragment, by which they are attached to mast cells and the Fab fragment, which remains free on the mast cells surface. The antigen will bind with the Fab fragment after repeated ingestion.

Thus, the key event of the immunological stage is the IgE synthesis and their attachment to mast cells. This process lasts 7-14 days and is called sensitization. After repeated ingestion, the allergen binds to the Fab fragment on the mast cells surface (the **pathochemical stage** (Figure 7.1 B) begins).

Depending on the time of release of allergy mediators, there are two phases of the pathochemical stage: early and late.

The early phase develops within a few seconds-minutes after repeated contact with the allergen. After the allergen binds to the IgE on the mast cell surface, it is activated and secretes mediators stored in the granules into the extracellular space. This process is called degranulation, and the mediators found in the granules are called preformed. These include the following substances:

Histamine, which has a different effect through the following receptors types:

H_1 - receptors-increased vascular permeability, smooth muscle spasm, irritation of nerve fibers, bronchiole contraction.

H_2 - receptors-increased secretory activity of the glands.

The eosinophil chemotaxis factor stimulates and activates the eosinophil chemotaxis. Eosinophils contain histaminase, which is necessary for the inactivation of histamine.

The neutrophil chemotaxis factor stimulates chemotaxis and neutrophil activation. Heparin is an anticoagulant that prevents blood clotting.

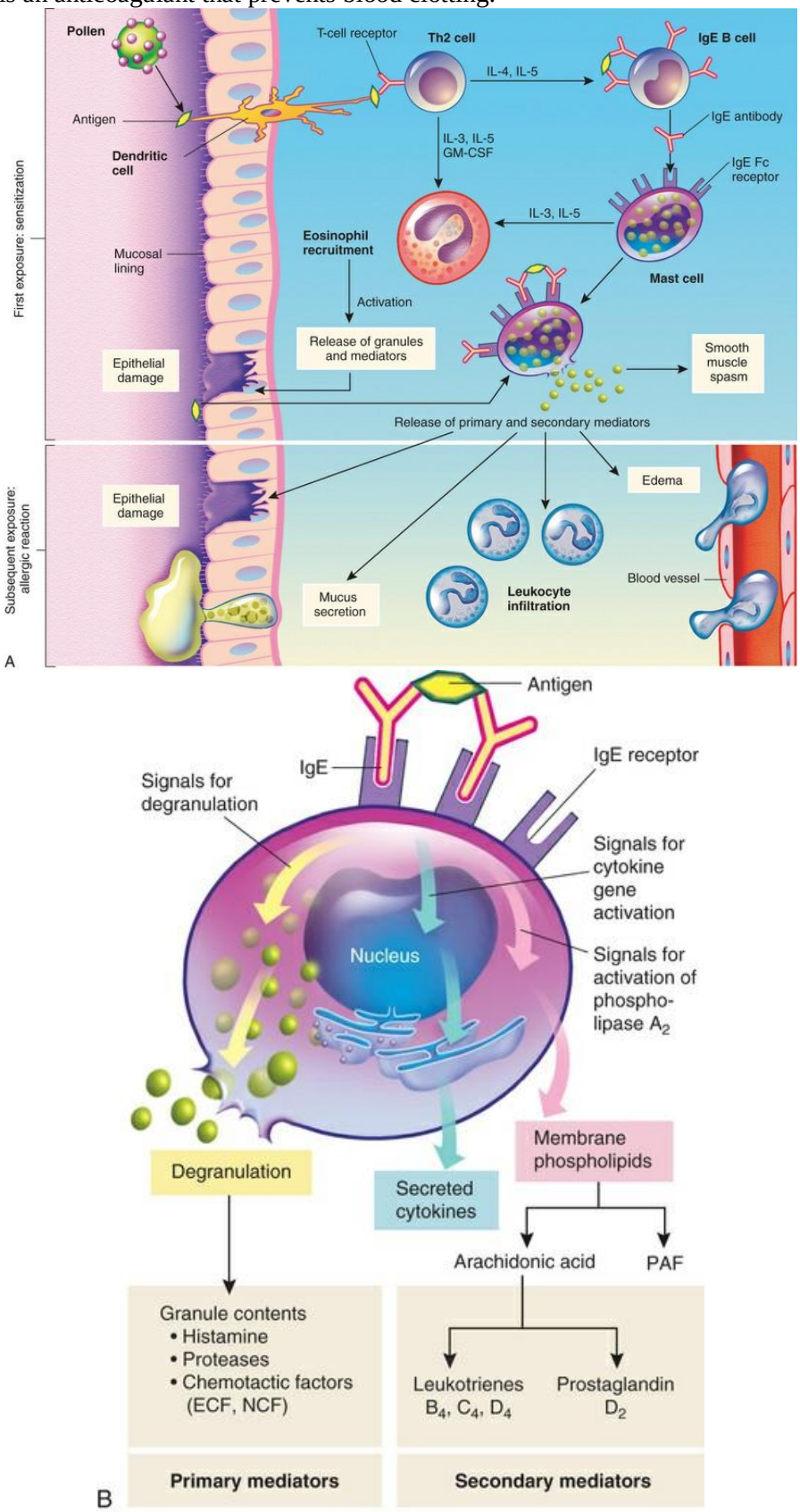

Figure 7.1 Mechanism of Type I IgE–Mediated Reactions. A, **The immunological stage**
B, **The pathochemical stage**
GM-CSF - Granulocyte-macrophage colony-stimulating factor, Fc - fragment crystallizable, Ig – immunoglobulin, IL – interleukin, NCF - neutrophil chemotactic factor, PAF - platelet-activating factor, Th

- T-helper. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

The late phase of the pathochemical stage is realized with the participation of mediators formed during the cleavage of arachidonic acid, which is part of the phospholipids of the mast cell membrane.

The cleavage of arachidonic acid occurs in two ways:

1. The cyclooxygenase pathway, which forms prostaglandins of different types (E_2, F_2, A_2). Prostaglandin F_2 and thromboxane A_2 cause spasm of the bronchi smooth muscles, prostaglandin E_2 is a bronchi dilator. Prostaglandins also help to increase the glands secretory activity.

2. The lipoxygenase pathway, which results in the formation of leukotrienes C4, D4, and E4. The complex of leukotrienes C4, E4, and D4 is called the slow-reacting substance of anaphylaxis. It causes smooth muscle spasm and increased vascular permeability.

In the **pathophysiological stage** (Figure 7.2), structural and functional disorders develop, which determine the clinical picture of allergic reactions.

Local manifestations of an allergic reaction depend on the site of the antigen penetration and include a reaction in the respiratory tract (mucosal edema, mucus hypersecretion, bronchospasm), in the gastrointestinal tract (abdominal pain, nausea, vomiting, diarrhea), skin (itching, swelling, rash, dermatitis).

Systemic manifestations of allergic reactions include anaphylactic shock. In this case, the allergen immediately enters the blood (injections of drugs, serums) and the vasoactive mediators release leads to systemic vasodilation.

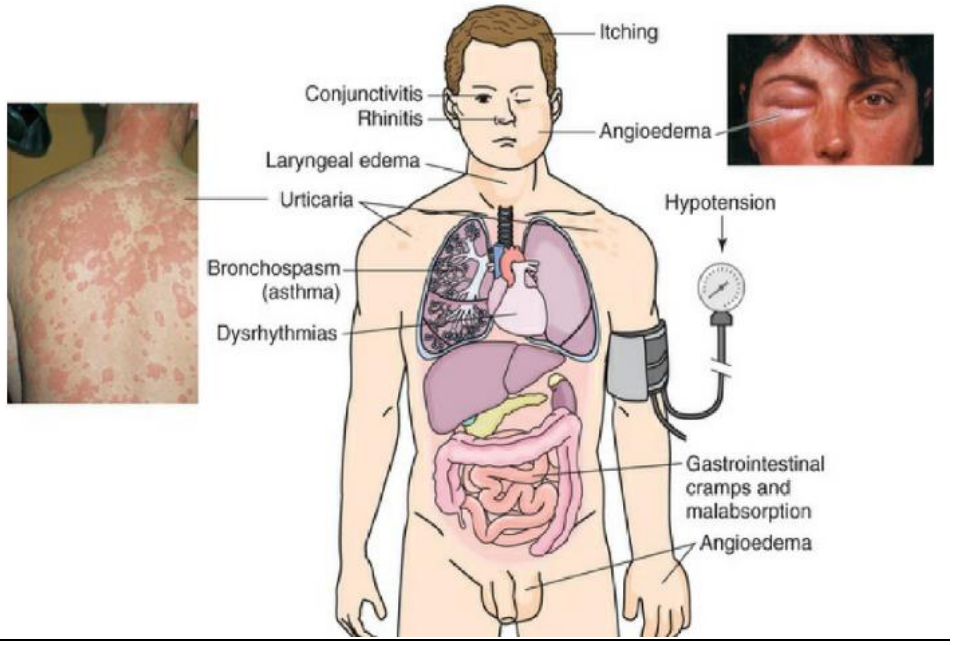

Figure 7.2. Mechanism of Type I IgE–Mediated Reactions. The pathophysiological stage (Inserts from Male D et al: Immunology, ed 8, St Louis, 2013, Mosby.)

Allergic reactions of type II (cytotoxic). Examples. Etiology, pathogenesis.

Allergic reactions of type II are associated with the cytotoxic effect of antibodies – immunoglobulins IgG, IgM. In this case the allergen is a hapten on the cell membrane, the cell membrane or extracellular matrix components. The antibodies cytotoxic effects are realized in three ways.

1. Complement-dependent cytolysis (Figure 7.3)

In the immunological stage, activated B-lymphocytes produce IgG, IgM antibodies, which attach to the allergen on the cell surface. The resulting antigen-antibody complex activates the complement system along the classical pathway to form a membrane-attacking cytotoxic complex of complement system proteins (C_5 – C_9), which destroys the cell with the allergen on the surface.

A classic example of complement-dependent cytolysis is hemolysis in blood transfusions that are incompatible with red blood cell antigens. The fixation of antibodies on the red blood cells surface leads to the complement system activation and the components of the membrane-attacking complex (C_5 – C_9) cause acute intravascular hemolysis.

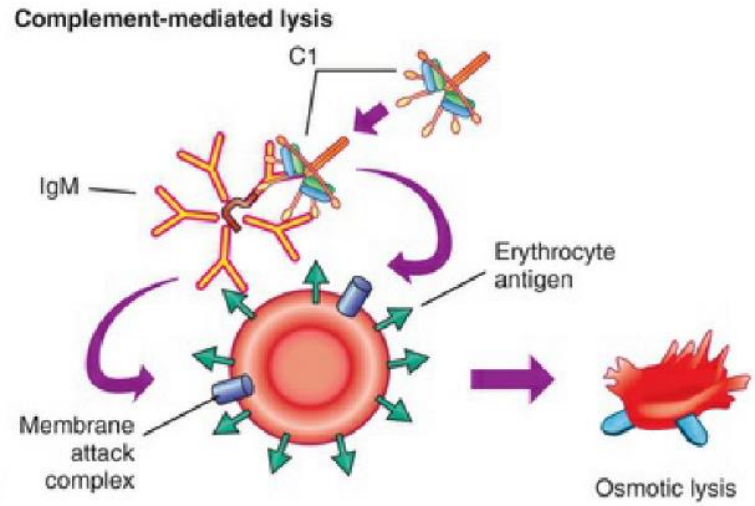

Figure 7.3 Mechanisms of Type II, Tissue-Specific, Reactions. Antigens on the target cell bind with antibody and are destroyed or prevented from functioning by complement-mediated lysis (an erythrocyte target). (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

2. Antibody-dependent phagocytosis (Figure 7.4)

In this case, mainly antibodies IgG_1 and IgG_3 are produced for the allergen, they interact with specific receptors on the surface of phagocytes (monocytes, macrophages, NK cells). These antibodies act as opsonins. They trigger the process of phagocytosis of the cell on the surface of which the allergen is located. An example of antibody-dependent cell cytolysis is autoimmune agranulocytosis, thrombocytopenic purpura, and Rh-conflict pregnancy.

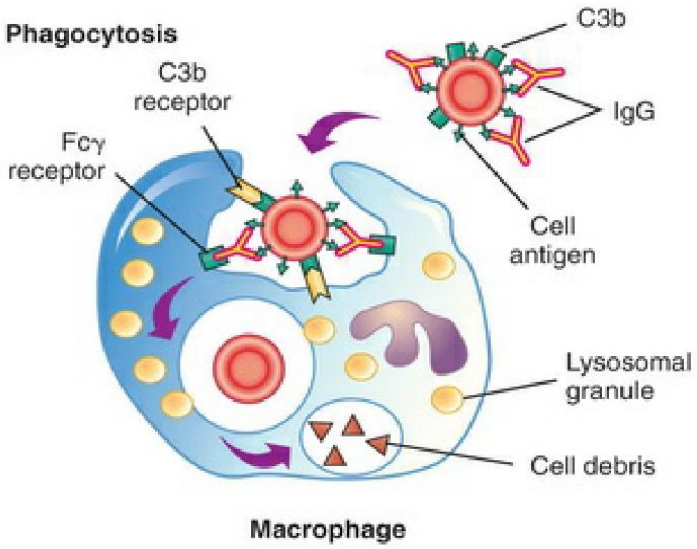

Figure 7.4 Mechanisms of Type II, Tissue-Specific, Reactions. Clearance (phagocytosis) by macrophages in the tissue. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

3. Antibody-dependent cellular cytotoxicity (Figure 7.6)

A cell with a hapten on the surface, covered with antibodies, is destroyed by cytotoxic cells (NK cells or cytotoxic lymphocytes) without the complement participation. The cells interact with the target cell by means of antibodies, which are connected by an antigen-binding site to the target cell surface, and by an Fc fragment to the killer cell. An example is Goodpasture's syndrome, in which IgG is deposited in the capillaries of the renal glomeruli, causing glomerulonephritis, and lung damage is characterized by bleeding.

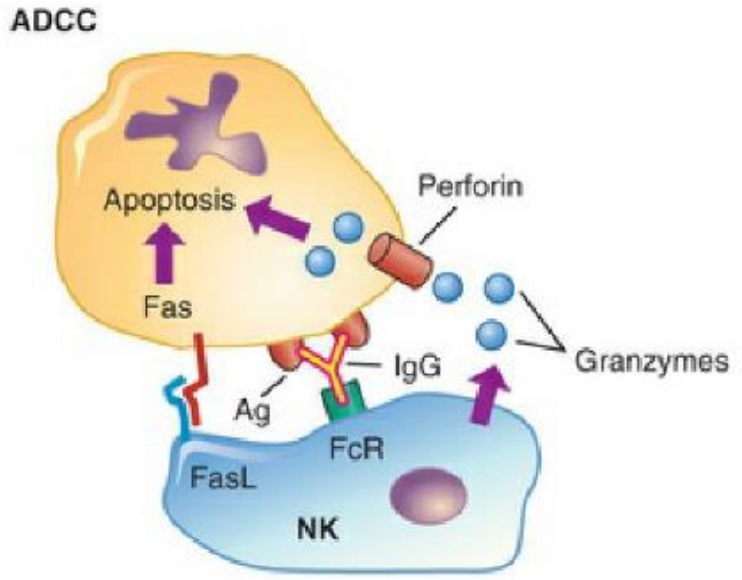

Figure 7.6 Mechanisms of Type II, Tissue-Specific, Reactions. Antibody-dependent cell-mediated cytotoxicity (ADCC) (apoptosis of target cells is induced by granzymes and perforin produced by natural killer [NK] cells and interactions of Fas ligand [FasL] on the surface of NK cells with Fas on the surface of target cells). (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Allergic reactions of type III (immunocomplex). Examples. Etiology, pathogenesis.

Allergic reactions of type III (Figure 7.7) are realized with the formation of immune complexes (antigen-antibody complexes). In this type of allergic reaction, the allergen is not fixed on the cell, but circulates freely in the plasma. In the immunological stage, after initial contact with the allergen, antibodies are formed - IgM, IgG, which form an antigen-antibody complex with it. In the case of an excess of antigen, these immune complexes cannot be completely removed by macrophages in the spleen or liver and the formation of circulating immune complexes (CIC) occurs, which are fixed on the vascular wall of the kidneys' glomeruli capillaries, as well as in the skin, joints, etc. organs. This causes the endothelium damage and activates the complement system, as well as macrophages, granulocytes, and platelets.

The complement system proteins are the main mediators of this allergic reaction type. Activation of complement system proteins leads to the immune inflammation development of the vessel wall. Anaphylotoxins C_{3a}, C_{5a} are chemoattractants, they attract neutrophils and monocytes to the immune complexes' accumulation sites, promote their activation and release of mediators and enzymes that damage the vascular wall. In turn, the $C_5 – C_9$ complement proteins can have a direct damaging effect on blood vessels.

Examples of type III hypersensitivity reactions are hemorrhagic vasculitis, glomerulonephritis, arthritis, serum sickness (develops after passive immunization with animal serum-based vaccines), allergic alveolitis, and Arthus reaction.

Allergic reactions of type IV (cell-mediated). Examples. Etiology, pathogenesis.

These allergic reactions occur according to the mechanism of delayed hypersensitivity (DHS). The key participants are T-lymphocytes and macrophages, and the maximum severity of manifestations is recorded after 3-5 days.

The development mechanism of the type IV allergic reaction (Figure 7.8) can be considered on the example of contact dermatitis. The allergen (nickel in jewelry, bracelets, components of medicines or cosmetics, latex in gloves, etc.) penetrates the skin and is phagocytized by skin macrophages (Langerhans cells), which then migrate to regional lymph nodes and present it to T-lymphocytes. T-lymphocytes are activated and differentiate into type I T-helper cells (Th_1 cells), after which they migrate to the site of contact with the allergen and, upon repeated contact, secrete pro-inflammatory cytokines that locally activate macrophages and attract monocytes to the site of contact. The local inflammatory process is clinically manifested in the form of dermatitis (Figure 7.9).

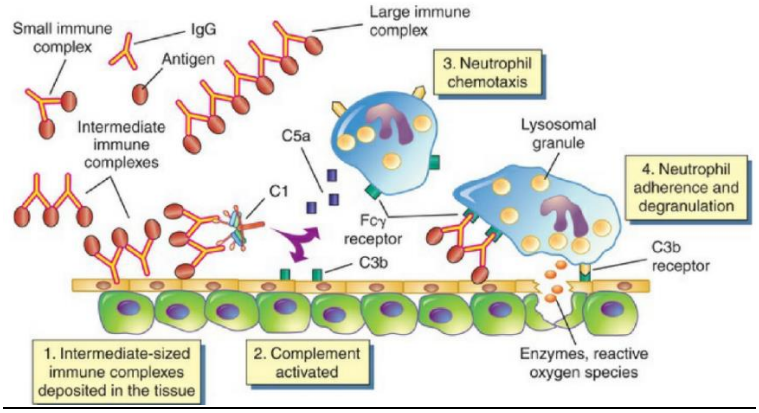

Figure 7.7 Mechanism of Type III, Immune Complex–Mediated, Reactions. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

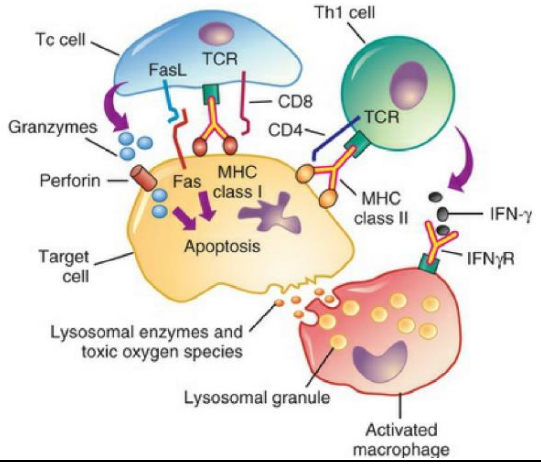

Figure 7.8 Mechanism of Type IV, Cell-Mediated, Reactions. T cells - Tc cells, helper T cells - Th1 cells, interferon-gamma - IFN-γ, IFN-γ receptor - IFNγR. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

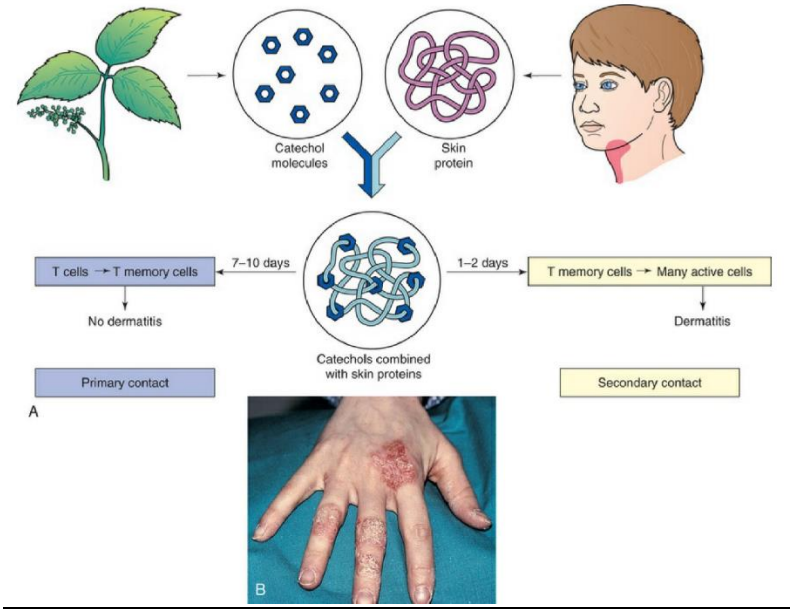

Figure 7.9 Development of Allergic Contact Dermatitis, a Delayed Hypersensitivity Reaction. A The development of allergy to catechols from poison ivy. B The contact dermatitis (From Damjanov I, Linder J: Anderson's pathology, ed 10, St Louis, 1996, Mosby.)

Pathogenesis of type V allergic reactions (Figure 7.10)

This type of allergic reaction is called antireceptor and develops according to the type of IHS. The allergen is the cell receptors. The autoimmune antibodies formation to allergens leads to stimulation or weakening of cell function. An example of the disease is myasthenia gravis, in which autoimmune blocking antibodies to the acetylcholine receptor are formed, which leads to a slowdown or disruption of the nerve impulse. An example of the stimulating effect of antibodies is the development of diffuse thyrotoxic goiter, in which the formation of autoantibodies – synergists to the thyroid-stimulating hormone receptor on thyroid cells is observed.

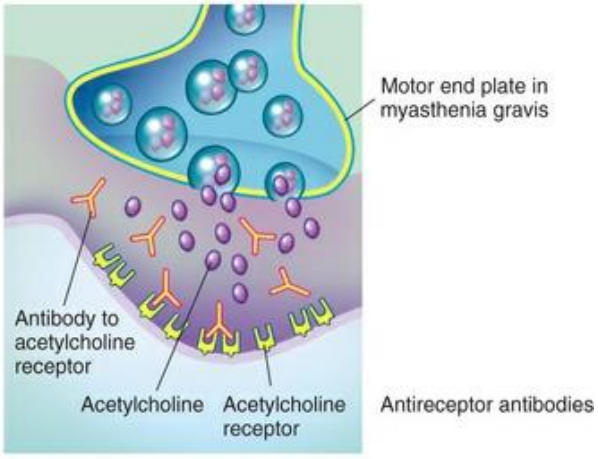

Figure 7.10 Mechanisms of Type V, Tissue-Specific, Reactions. modulation or blocking the normal function of receptors by antireceptor antibody. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Practical lesson 8. Pathophysiology of the immune system. Immunodeficiencies: primary and secondary. Autoimmune diseases

Key questions of the session:

1. Autoimmune diseases: definition, etiology, pathogenesis, examples.
2. Primary immunodeficiency states. Etiology, pathogenesis, examples.
3. Secondary immunodeficiency states. Etiology, pathogenesis, examples.

Autoimmune diseases: definition, etiology, pathogenesis, examples.

Autoimmune diseases originate from the coincidence of an initiating event in a genetically predisposed individual leading to an autoimmune mechanism that affects specific target tissues or cells (Figure 8.1).

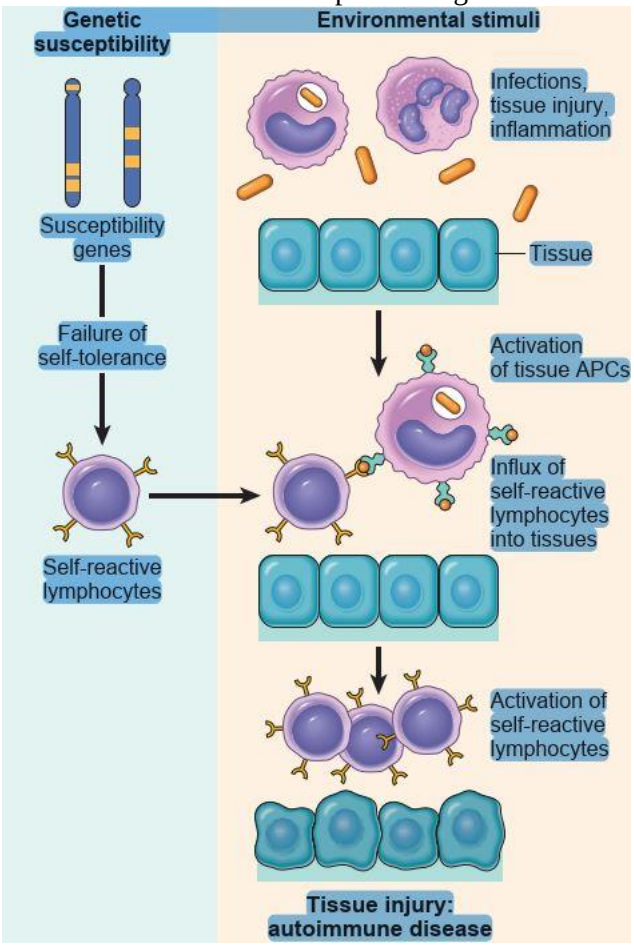

Figure 8.1 Pathogenesis of autoimmunity. Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (such as infections, tissue injury, and inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage

Some autoimmune diseases can be familial and attributed to the presence of a very small number of susceptibility genes. Affected family members may not all develop the same disease, but have different disorders characterized by a variety of hypersensitivity reactions, including autoimmune and allergic. For instance, the Human Leukocyte Antigen B27 (Human Leukocyte Antigen is discussed further under Transplantation and Transfusion) is a risk factor for developing ankylosing spondylitis (AS), an autoimmune inflammatory disease of the spine. Ninety-five percent of individuals diagnosed with AS express Human Leukocyte Antigen-B27, whereas only 4% to 8% of the general population expresses this antigen. Although most autoimmune diseases appear as isolated events without a positive family history, susceptibility for developing such diseases appears to be linked to a combination of multiple genes.

Autoimmune reactions may be triggered by infections. Two mechanisms have been postulated to explain the link between infections and autoimmunity (Fig. 8.2). First, infections may upregulate the expression of costimulators on APCs. If these cells are presenting self antigens, the result may be a breakdown of anergy and activation of T cells specific for the self antigens. Second, some microbes may express antigens that have the same amino acid sequences as self antigens. Immune responses against the microbial antigens may result in the

activation of self-reactive lymphocytes. This phenomenon is called molecular mimicry. A clear example of such mimicry is rheumatic heart disease, in which antibodies against streptococcal proteins cross-react with myocardial proteins and cause myocarditis. More subtle molecular mimicry may be involved in classic autoimmune diseases as well. Microbes may induce other abnormalities that promote autoimmune reactions. Some viruses, such as Epstein-Barr virus (EBV) and HIV, cause polyclonal B-cell activation, which may result in production of autoantibodies. The tissue injury that is common in infections may release self antigens and structurally alter these antigens so that they are able to activate T cells that would not be tolerant to these new, modified antigens. Infections may induce the production of cytokines that recruit lymphocytes, including potentially self-reactive lymphocytes, to sites of self antigens.

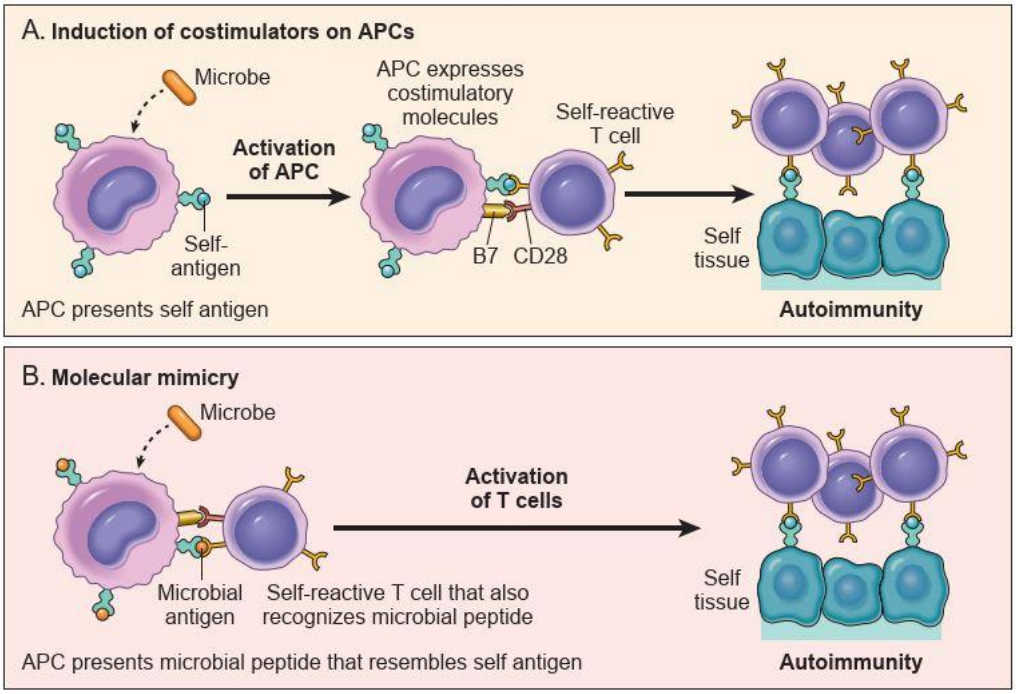

Figure 8.2 Postulated role of infections in autoimmunity. Infections may promote activation of self-reactive lymphocytes by inducing the expression of costimulators (A), or microbial antigens may mimic self antigens and activate self-reactive lymphocytes as a cross-reaction (B)

Many examples of autoimmune diseases have been described. Most of the classic autoimmune diseases, including disorders of the endocrine system (autoimmune thyroiditis and Graves disease), hematologic system (the hemolytic and pernicious anemias), nervous system (myasthenia gravis), and connective tissue in joints (rheumatoid arthritis). Several basic principles are exemplified by one example: systemic lupus erythematosus. Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory disease and is one of the most common, complex, and serious of the autoimmune disorders. SLE is characterized by multiple immune disorders that result in the production of a large variety of autoantibodies against nucleic acids, erythrocytes, coagulation proteins, phospholipids, lymphocytes, platelets, and many other self-components (Fig 8.3). The most characteristic autoantibodies produced in SLE are against nucleic acids (e.g., single-stranded deoxyribonucleic acid [DNA], double-stranded DNA), histones, ribonucleoproteins, and other nuclear materials. Deposition of circulating immune complexes containing antibody against DNA produces tissue damage in individuals with SLE. DNA and DNA-containing immune complexes have a high affinity for glomerular basement membranes and therefore may be selectively deposited in the glomerulus. The presence of DNA in the circulation increases from cellular damage in response to trauma, drugs, or infections and is usually removed in the liver. Removal of circulating DNA is slowed in the presence of immune complexes, thereby increasing the potential for deposition in the kidney. Deposition of immune complexes composed of DNA and antibody also causes inflammatory lesions in the renal tubularbasement membranes, brain (choroid plexus), heart, spleen, lung, gastrointestinal tract, skin, and peritoneum. SLE, as with most autoimmune diseases, occurs more often in women (approximately a 10 : 1 predominance of females), especially in the 20- to 40-year-old age group. Blacks are affected more often than whites (about an eightfold increased risk). A genetic predisposition for the disease has been implicated on the basis of increased incidence in twins and the existence of autoimmune disease in the families of individuals with SLE. Clinical manifestations of SLE include arthralgias or arthritis (90% of individuals), vasculitis and rash (70% to 80% of individuals), renal disease (40% to 50% of individuals), hematologic abnormalities (50% of individuals, with anemia being the most common complication), and cardiovascular diseases (30% to 50% of individuals). A

recent study of male and female individuals with SLE reported gender-based differences in the incidence of SLE-related symptoms. Females more commonly developed alopecia, photosensitivity, oral ulcers, malar rash, lupus anticoagulant, arthritis, and serositis with pleurisy, whereas males more commonly developed thrombocytopenia, anti-dsDNA, and renal involvement. As with most autoimmune diseases, the disease process develops slowly (up to 10 years from occurrence of the first autoantibody until diagnosis) and is characterized by frequent remissions and exacerbations. Because the signs and symptoms affect almost every body system and tend to be intermittent, SLE is extremely difficult to diagnose. Laboratory diagnosis is usually based on a positive ANA screening test; about 98% of persons with SLE are positive, but a substantial number of false-positives occur in healthy individuals and those with other diseases. Because SLE is a progressive and slowly developing disease, some laboratory tests, including the ANA, may be positive years before the onset of clinical symptoms. Detection of a positive ANA is usually followed by one or more specific tests (e.g., antibodies against Sm, dsDNA) that are complicated by low sensitivity (only a portion of individuals with SLE will be positive, although the number of false-positives is low).

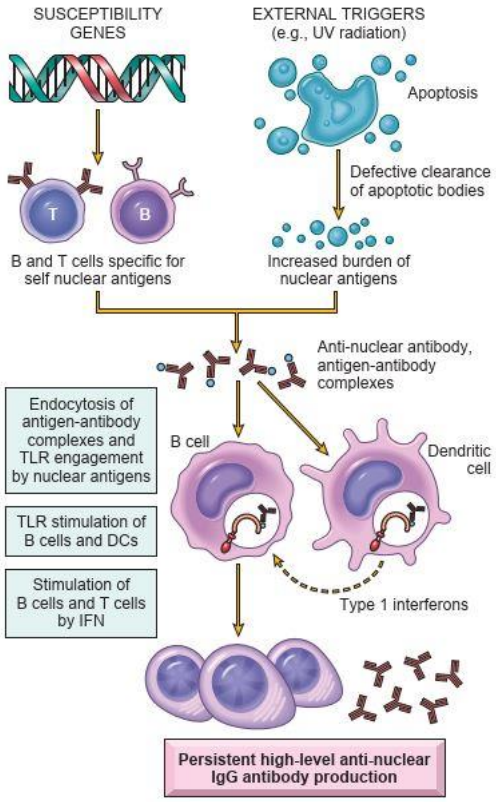

Figure 8.3 Model for the pathogenesis of systemic lupus erythematosus. In this hypothetical model, susceptibility genes interfere with the maintenance of self-tolerance and external trigger lead to persistence of nuclear antigens. The result is an antibody response against self nuclear antigens, which is amplified by the action of nucleic acids on dendritic cells (DCs) and B cells, and the production of type 1 interferons. TLRs, Toll-like receptors.

Primary immunodeficiency states. Etiology, pathogenesis, examples

Primary immunodeficiencies are genetically determined diseases caused by a violation of a complex cascade of reactions necessary for the elimination of foreign agents from the body and the development of adequate inflammatory reactions (Fig 8.4).

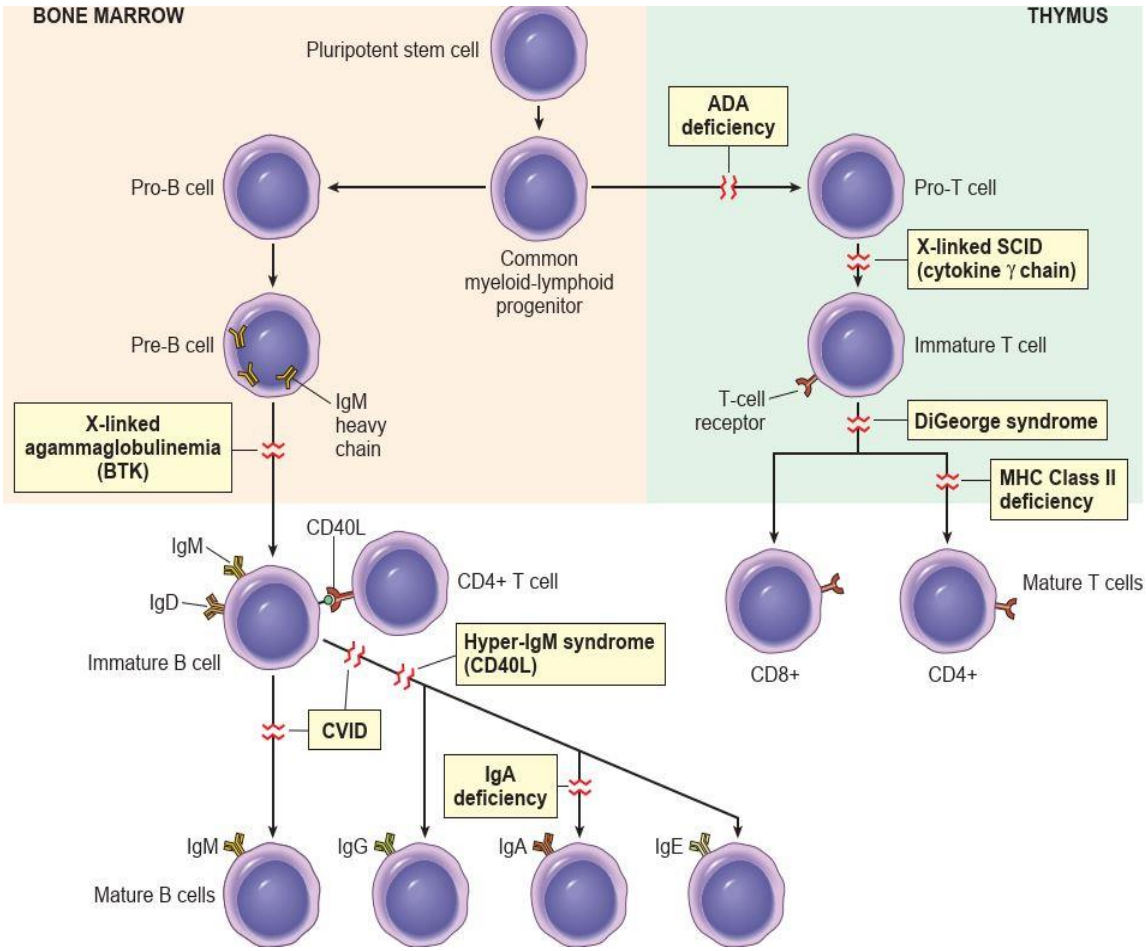

Figure 8.4 Primary immune deficiency diseases. Shown are the principal pathways of lymphocyte development and the blocks in these pathways in selected primary immune deficiency diseases. The affected genes are indicated in parentheses for some of the disorders. ADA - Adenosine deaminase; CD40L - CD40 ligand (also known as CD154); CVID - common variable immunodeficiency; SCID - severe combined immunodeficiency

In approximately 60% of the cases, symptoms of immune deficiency appear within the first 2 years of life, whereas other immune deficiencies are progressive, with the onset of symptoms appearing in the second or third decade of life. The most common symptoms include sinusitis (68% of individuals), pneumonia (51%), ear infections (51%), diarrhea (30%), and bronchitis (55%), with the incidence varying depending on the specific syndrome.

According to the violation of the link of immunity, primary immunodeficiencies are divided into four groups:

1. T-cell immunodeficiencies - deficiency of the cellular component of immunity.
2. B-cell immunodeficiencies - a violation of the humoral link of immunity.
3. Combined immunodeficiencies - a violation of both cellular and humoral links.
4. Violations of innate immunity caused by a defect in phagocytosis and the complement system.

T-cell immunodeficiencies are characterized by impaired function of T-lymphocytes, with relatively preserved functions of B-lymphocytes. An example of T-cell immunodeficiency is Di George's syndrome - congenital hypoplasia (developmental disorder) of the thymus gland. Di George's syndrome occurs as a result of deletion of chromosome 22 and is characterized by a violation of the thymus anlage, heart defects, hypocalcemia, and the presence of a defect in the maxillofacial region - palatine cleft. Patients with T-cell immunodeficiency are characterized by a tendency to a chronic course of infections caused by viruses and intracellular parasites, cancer (due to a violation of antitumor immunity).

B-cell immunodeficiencies are associated with a defect in the formation of antibodies (immunoglobulins of various classes) by plasma cells. Plasma cells are formed from B-lymphocytes (blast-transformation reaction) after their activation by T-lymphocytes Examples of B-cell immunodeficiencies: X-linked agammaglobulinemia (Bruton's agammaglobulinemia), selective immunoglobulin A deficiency (Yow's syndrome), hyper-immunoglobulin M. Patients with B-cell immunodeficiency are prone to infections of the ENT organs and the respiratory system.

Combined immunodeficiencies are the most common. These include: the Swiss type of hypogammaglobulinemia, Louis-Bar, Wiskott-Aldrich syndromes (in combination with thrombocytopenia, eczema, splenomegaly), etc. However, in combined immunodeficiencies, the leading role belongs to the defect of T cells.

Violation of phagocytic activity can be associated with a violation of any of the stages of phagocytosis: chemotaxis, adhesion, keeling or destruction of the phagocytosis object. Examples of impaired phagocytic activity are: "naked lymphocyte" syndrome (there are no class II and / or class I HLA antigens on the membrane of lymphocytes and macrophages), deficiency of adhesion molecules on the surface of leukocytes, microtubule disorder (Chediak-Higashi syndrome), chronic agranulomatosis (lytic enzymes). Patients with impaired phagocytosis are characterized by a tendency to pustular lesions of the skin and mucous membranes.

A defect in the complement system is the suppression of synthesis or the complete absence of any component of the complement system. It is manifested by a tendency to recurrent infections or immunocomplex pathology (systemic lupus erythematosus).

Secondary immunodeficiency states. Etiology, pathogenesis, examples

Secondary immunodeficiencies are disorders of immunity resulting from somatic and other diseases, as well as external factors (Table 8.1).

Table 8.1 Examples of secondary immune deficiencies

Cause of deficiency	Examples
Normal physiologic Conditions	Pregnancy Premature infants Infancy Aging
Psychologic stresses	Emotional trauma Eating disorders
Dietary insufficiencies	Protein-calorie malnutrition Protein loss syndromes (e.g., nephrotic syndrome, protein-losing enteropathy) Vitamin deficiencies
Malignancies	Hematologic malignancies (e.g., Hodgkin disease, acute or chronic leukemia, myeloma) Solid tumors (e.g., sarcomas, carcinomas)
Chronic diseases	Diabetes Cystic fibrosis Alcoholic cirrhosis Sickle cell disease Aplastic anemia Autoimmune diseases (e.g., systemic lupus erythematosus)
Chromosome Abnormalities	Trisomy 21 (Down syndrome)
Environmental agents	Ultraviolet light Ionizing radiation Chronic hypoxia
Physical trauma	Burns
Medical treatments	Stress from surgery Anesthesia Immunosuppressive treatments (e.g., corticosteroids, antilymphocyte antibodies) Splenectomy Anticonvulsive medications Cancer treatment (e.g., cytotoxic drugs, ionizing radiation)

	Hematopoietic stem cell transplants
Infections	Congenital inflections (e.g., rubella, cytomegalovirus, hepatitis B) Acquired infections (e.g., AIDS)
Lifestyle	Alcohol abuse

Normal Physiologic Conditions. The competence of an individual's immune system varies throughout life. Pregnancy itself is considered by many to be an immunocompromised condition. Pregnant women may have decreased reactivity or altered results in several tests of the immune system, including skin tests against various antigens, circulating numbers of T lymphocytes, and other very general tests. Pregnancy itself, however, is not associated with a marked change in infections, suggesting that the mother's immune system is not severely altered. The newborn child is immunologically immature. Although T-cell immune responses may be normal or near normal, other components of the immune system (especially antibody production) are just beginning to mature. Beginning at about 32 weeks of pregnancy, the placenta transports maternal antibodies into the fetal blood to protect the child during the first months of life. After the delivery, the level of the mother's antibodies slowly decreases in the newborn so that maternal antibodies no longer protect the child by about 6 months of life. By 6 to 8 months, the newborn should be efficiently protected by antibodies produced by its own B cells. In some infants, the development of antibody production is delayed, and a transient low level of antibody may persist for several months (transient hypogammaglobulinemia of infancy), during which the child has increased susceptibility to infections. Premature infants are particularly immunologically immature and are at increased risk for neonatal infections. The blood of infants born before 32 weeks' gestation is generally devoid of maternal antibody. However, if the infant is born prematurely, the degree of immunologic immaturity is greater and places the child at a significant risk of developing infections. Aging is also associated with a progressive depression in immune responses. Older adults generally have more severe bacterial and fungal infections, greater difficulty resolving those infections, and lower responses to vaccination. Several meaningful changes occur during aging, although variations in the degree of change and a corresponding increased susceptibility to infection can be considerable among individuals. The thymus involutes over time, resulting in decreased production of fresh T cells. A concurrent depletion of T-memory cells results in depressed responses to both new and “recall” antigens. A shift toward Th2 cells also may occur with a resultant decrease in Th1 cytokines. Total numbers of B cells may decrease. Numbers of NK cells may remain normal, although their activity is decreased. Similarly, neutrophil numbers may remain normal, with decreased phagocytosis and killing.

Psychologic Stress. The relationship between emotional stress and depressed immune function has become an area of intense clinical and research interest. For many decades anecdotal reports have suggested that increased incidences of infection and malignancy are associated with periods of both intense stress (e.g., the loss of a loved one, divorce) and relatively minor stress (e.g., final examination periods at colleges and universities). In addition, early studies showed that immune function, as demonstrated by delayed hypersensitivity skin test results, could be depressed through posthypnotic suggestion. The mechanisms of the relationship between emotional stress and the immune system are now beginning to be understood. Many lymphoid organs are innervated and can be affected by nerve stimulation. In addition, lymphocytes have receptors for many hormones (e.g., sex hormones, neurotransmitters, and neuropeptides) and can respond to changing levels of these chemicals with increased or decreased function. For instance, stress-induced catecholamines affect the expression of adhesion molecules and the movement of lymphocytes among lymphoid organs.

Dietary Insufficiencies. Nutritional status can have a profound effect on immune function, and malnutrition is the predominant cause of secondary immune deficiencies worldwide. Severe deficits in protein or calorie (protein-calorie malnutrition) intake lead to immune deficiencies. Marasmus (deficiency in calories) and kwashiorkor (deficiency in protein, but adequate calories) have similar outcomes. T-cell rich areas of primary (thymus) and secondary lymphoid tissue are greatly affected, resulting in impaired T-cell function. Antibody levels are normal but neutrophil function (chemotaxis, phagocytosis, bacterial killing), complement levels, and NK activity are impaired, resulting in infections with microorganisms that are normally destroyed by opsonization and phagocytosis. Deficient zinc intake can profoundly depress both T- and B-cell function. Zinc is required as a cofactor for at least 70 different enzymes, some of which are found in lymphocytes and are necessary for their function. Secondary zinc deficiencies may be associated with malabsorption syndrome (failure to absorb zinc), chronic renal disease (loss of zinc in the urine), chronic diarrhea (loss of zinc through the gut), or burns or severe psoriasis (loss of zinc through the skin). Deficiencies of other enzyme cofactors, such as vitamins (e.g., pyridoxine, pantothenic acid, folic acid, and vitamins A, C, E, and B12), also may result in severe depressions of B- and T-cell function, phagocytosis, and complement activity.

Malignancies. Many malignancies are complicated by a wasting syndrome (cachexia) in the later stages, which can suppress the immune system secondary to the resultant malnutrition. The effect is commonly nonspecific, resulting in a generalized deficiency of the immune response and a greatly increased susceptibility to developing life-threatening infections. In fact, many people with malignancies die from infection rather than from direct effects of the tumor. Other malignancies (e.g., lymphomas, leukemias, plasmacytomas) present with an early and more specific immune depression. Non-Hodgkin lymphoma may result in an antibody deficiency in the most advanced stages of the disease. Hodgkin lymphoma, however, may suppress the immune system even before the onset of symptoms, with worsening of the suppression as the disease progresses. Individuals usually present with depletion of T cells with normal production of T-cell–independent antibodies. In general, leukemia is characterized by normal T- and B-cell responses until progression to terminal stages. Chronic lymphocytic leukemia commonly suppresses B-cell differentiation but does not affect T-cell function. Depressed production of antibodies results in increased susceptibility to fatal infection. Plasmacytomas (malignancies of plasma cells) result in greatly diminished antibodies because the malignant cells are displacing normal plasma cells and increased catabolism of immunoglobulins results in increased susceptibility to infections against which antibody is protective. T-cell immunity remains intact.

Chronic Diseases. Chronic diseases of the cardiovascular, gastrointestinal, and renal systems are commonly complicated by a secondary immune suppression. Nephrotic syndrome from inflammation of the kidneys results in loss of protein through the kidneys, proteinuria (increased protein in the urine), and resultant hypoproteinemia (diminished protein in the blood). The loss of IgG may increase susceptibility of infection. Protein-losing enteropathy results from conditions that damage the surface of the gastrointestinal tract (e.g., inflammatory bowel diseases, such as Crohn disease, ulcerative colitis, celiac

disease, gastrointestinal [GI] infections, cancer of the GI tract). Although circulating levels of immunoglobulin are diminished because of loss through the GI tract and catabolism, increased susceptibility to infections is rare.

Metabolic Diseases or Genetic Syndromes. Diabetes results in altered glucose metabolism and suppresses many aspects of the immune and inflammatory responses, including phagocytosis and chemotaxis, and lymphocyte proliferation. The effects of trisomy 21 are less severe, but primarily include diminished neutrophil function. People with cystic fibrosis have decreased airway clearance of bacteria, thus increasing the probability of major respiratory tract infections.

Environmental Agents. Individuals are constantly exposed to environmental agents that affect the immune system. UV light from sun exposure or tanning salons induces apoptosis of lymphoid stem cells, increases production of Treg cells that suppress defenses against cancer, and increases production of antiinflammatory cytokines.

Physical Trauma. Trauma that compromises the epithelial barrier also predisposes an individual to infection. Burn victims are susceptible to severe bacterial infections. Thermal burns appear to be associated with suppressed neutrophil function (especially chemotaxis), complement levels, cell-mediated immunity, and primary humoral responses, although secondary humoral responses are normal. The mechanism of this immunosuppression may be twofold. Blood from burned individuals contains nonspecific immunosuppressive factors (all immune responses are suppressed, regardless of the antigen involved). In addition, burn victims also have increased regulatory T-cell function, which may increase antigen-specific suppression.

Medical Treatments. Medical treatments themselves may produce suppression of immune responses. Surgery and administration of anesthesia can suppress T-and B-cell function. Transient, severe lymphopenia (loss of circulating lymphocytes) is a common postoperative condition that can last as long as a month. Surgery to remove the spleen (splenectomy) can result in a depressed IgM response against encapsulated bacteria (especially S. pneumoniae, H. influenzae, Staphylococcus aureus, Group A streptococci, and Neisseria meningitidis) and decreased levels of opsonins. Corticosteroids are intentionally used to suppress the immune system and control hypersensitivity diseases (especially autoimmune disease) or prevent rejection of transplants. They predominantly inhibit T-cell function, prevent lymphocyte proliferation, inhibit production of critical cytokines, and suppress monocyte/macrophage functions; but they do not affect neutrophils. Because of their nonspecific activity, however, immune responses against infectious agents also can be suppressed, increasing an individual's susceptibility to infection. Many drugs and other treatments that are used to fight cancer (e.g., cytotoxic cancer chemotherapeutic agents, irradiation) are not specific for cancer cells, but are designed to attack cells in susceptible stages in their cell cycles or rapidly proliferating cells, which includes cells of the immune system as well as malignant cells. Cytotoxic agents may affect all lymphocyte subsets or may only affect a specific stage of the immune response. For instance, azathioprine and methotrexate affect response after antigenic challenge, whereas cyclophosphamide affects response before and after exposure to antigen. Cyclosporine A preferably affects CD4+ cells. The immunosuppressive effects of chemotherapeutic drugs are exacerbated by concurrent

treatment with ionizing radiation (x-rays), which also affects rapidly dividing cells. T-cells, particularly CD4+ cells, are most sensitive. Phagocytes, which

have a much slower proliferation rate, are relatively resistant to the effects of irradiation. Depending on the dose of irradiation administered, the entire immune system may be depleted. The list of medications that affect the immune response is ever increasing and includes analgesics, antithyroid medications, anticonvulsants, antihistamines, antimicrobial agents, antilymphocyte antibodies, and tranquilizers.

Infections. Many infectious microorganisms successfully invade the human body using mechanisms for fighting off specific immune/inflammatory responses against themselves. However, some infectious agents more broadly suppress the immune response. Human immunodeficiency virus (HIV) is one of the few microorganisms that directly attacks the central processes involved in the development of an immune response. It infects and destroys the T-helper cell, which is necessary to provide help for the maturation of both plasma cells and T-cytotoxic cells. Therefore, HIV suppresses the immune response against itself and secondarily creates a generalized immune deficiency by suppressing the development of immune responses against other pathogens and opportunistic microorganisms. Several other viruses (e.g., measles; hepatitis B; and herpes viruses, such as Epstein-Barr virus [EBV], cytomegalovirus [CMV], and herpes simplex viruses) may suppress various components of the immune response. CMV, herpes virus, and hepatitis B virus in particular can establish congenital infections through transmission from an infected mother to the child in utero or at birth when the child's immune system is immature. These children may have suppressed immune responses, although the degree of the deficiency is not usually severe. However, as the child's immune system develops, the viral antigens may be partially seen as “self” so that a chronic infection is established. Measles virus can infect both B and T cells and macrophages. Infection may result in lymphopenia and a suppressed T-cell response that are generally transient. Acute infections with herpes viruses may transiently suppress the immune system. EBV infects B cells and may cause infectious mononucleosis, although most EBV infections are asymptomatic. The virus enters a stage of latency in memory B cells. In some cases, EBV may suppress both CD4+ and CD8+ T cells and NK cells. Immunosuppression is generally transient and not severe. CMV infects mucosal epithelium and can infect macrophages where antigen processing and presentation may be impaired. Other infections may lead to a relatively broad suppression of immune responses. Mycobacterium leprae causes two forms of leprosy: tuberculoid leprosy, in which an active T-cell immunity contains and kills the infecting bacteria; and lepromatous leprosy, in which the infected individual's T-cell immunity is severely depressed but high levels of antibody are produced. The T-cell deficit is characterized by suppressed T-cell IL-2 production and antigen-specific T-cell responses. Some fungal infections may suppress the immune response. In disseminated Candida albicans infections, T-cell responses and neutrophil chemotaxis are suppressed to various degrees. Similar immunosuppression may be observed in individuals with disseminated histoplasmosis (infections with Histoplasma capsulatum). The most severe form of acute malaria (caused by the parasite Plasmodium falciparum) suppresses specific antibody responses against protein and polysaccharide antigens by dysregulation of CD4+ T-cell function and decreased IL-2 production.

Practical lesson 9. Fever. Hyperthermia. Hypothermia.

Key questions of the lesson

1. The thermoregulation processes in the body are normal.
2. Fever: definition, etiology, pathogenesis.
3. Changes in the metabolism, function of organs and systems in fever.
4. The biological significance of fever. The concept of pyrotherapy.
5. Characteristics of the acute phase response concept. Mediators of the acute phase response. Pathogenesis of manifestations.
6. Hyperthermia: definition, etiology, classification, pathogenesis. Differences between overheating and fever.
7. Hypothermia: definition, etiology, pathogenesis. The use of artificial hypothermia in medicine.

The thermoregulation processes in the body are normal.

Thermoregulation is the process of maintaining the body temperature at a constant level, regardless of fluctuations in the ambient temperature.

From the position of thermoregulation in the human body, a thermal "core" and a thermal "shell" are distinguished. The "shell" consists of skin, skeletal muscles, mucous membranes, it is characterized by the predominance of heat transfer processes over heat production. The "core" includes the organs of the thoracic cavity, abdominal cavity, deep muscles, spinal cord and brain, it is characterized by the predominance of heat production processes over heat transfer. The temperature of the" core " of the body is constant and is maintained at 37.1°C. Thermoregulation in the body is carried out by means of heat production, heat transfer, behavior changes (Figure 9.1).

The afferent link of thermoregulation is represented by thermoreceptors. Peripheral thermoreceptors are located in the tissues of the thermal "core" and the thermal "shell". The pulses from them are sent to the thermoregulatory center. Peripheral thermoreceptors are more sensitive to cold than to heat. The central thermoreceptors are located in the thermoregulatory center itself.

The central link of thermoregulation is represented by the preoptic region of the anterior hypothalamus (PRAH) and the posterior hypothalamus. The PRAH contains the heat transfer center, central thermoreceptors, insertion neurons, and reference neurons. The reference neurons form a standard comparison signal, and their activity corresponds to the temperature setting point. **The temperature setting point** is the temperature of the hypothalamus itself, at which the processes of heat production and heat transfer are balanced. If the activity of the insertion neurons corresponds to the activity of the reference neurons, then the processes of heat production and heat transfer are balanced, and the temperature of the thermal "core" is maintained at 37.1 °C. In the posterior part of the hypothalamus is the center of heat production and the body of neurons of peripheral thermoreceptors.

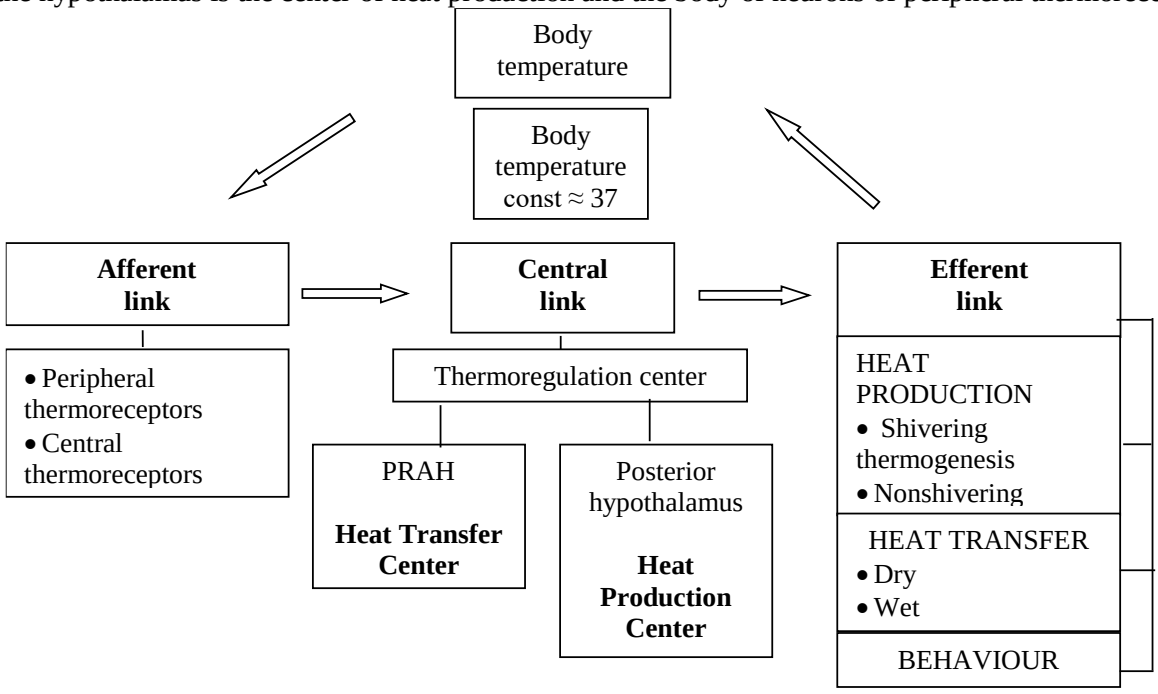

Figure 9.1 Body temperature regulation scheme

Efferent link of thermoregulation

1. The change in heat production is realized due to contractile thermogenesis (physical heat production), the release of heat during muscle contraction and non-contractile (chemical) thermogenesis, which includes a complex of biochemical processes occurring in the tissues of internal organs (brain, liver, lungs).

2. The change in the heat transfer process is realized due to the" dry "heat transfer by the body through heat radiation, thermal conductivity and convection, and" wet " heat transfer by evaporation of heat from the surface of the skin and mucous membranes of the airways.

3. The change in human behavior is realized through the choice of clothing, the regulation of the air temperature in the room, the search for a comfortable area.

Fever: definition, etiology, pathogenesis.

Fever is a typical pathological process,

- arising in response to the action of pyrogens,
- characterized by a dynamic restructuring of the thermoregulation center to another, higher level,
- manifested by an increase in temperature above normal, regardless of the ambient temperature.

The etiological factor of fever is **pyrogen.**

1. Exogenous (primary) pyrogens

* Infectious: lipopolysaccharide (lipoid A) of the gram-negative bacteria cell wall, lipoteichoic acids of gram-positive bacteria, peptidoglycans, components of viruses, rickettsias, chlamydia, mycoplasma, spirochetes.

* Non-infectious: whole blood, sera, vaccines, tissue components with aseptic damage (heart attack, necrosis, hemolysis).

2. Endogenous (secondary) pyrogens are formed in phagocytes under the influence of primary pyrogens: IL-1, IL-6, tumor necrosis factor-α, interferron-γ.

Pathogenesis of fever

1. The stage of the rise (increase) of body temperature (stadium incrementi).
2. The stage of standing body temperature (stadium fastigii).
3. The stage of reducing body temperature (stadium decrementi).

Stage 1. The increase in temperature is due to the predominance of heat production over heat transfer. Primary pyrogens stimulate the synthesis and secretion of secondary pyrogens by neutrophils and macrophages. With the blood flow, endogenous pyrogens reach the brain and interact with the receptors of the reference neurons of the thermoregulatory center in the preoptic region of the anterior hypothalamus. In the reference neurons, phospholipase A_2 is activated, arachidonic acid is synthesized as a substrate for the cyclooxygenase pathway, the product of which is, among other things, prostaglandin E_2, which changes the activity of the reference neurons and thereby leads to a shift of the thermostatic point to a higher level. There is a mismatch between the activity of the reference neurons (the thermal setting point) and the activity of the insertion neurons (the integrated signal from the peripheral and central thermoreceptors). As a result, the center of heat production is activated and the activity of the center of heat transfer decreases, followed by an increase in body temperature.

The antipyretic effect of acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs is due to their ability to inhibit the activity of the cyclooxygenase enzyme, i.e. to block the formation of prostaglandin E2 from arachidonic acid.

In adults, the greatest importance in increasing body temperature belongs to the restriction of heat transfer, and not to an increase in heat production. In children, on the contrary, an increase in heat production comes to the fore. The restriction of heat transfer occurs due to the narrowing of the peripheral vessels and a decrease in blood flow to the tissues. There is a muscle tremor, a feeling of chills. The most important thing is the spasm of the skin vessels and the cessation of sweating. The skin turns pale, its temperature decreases, and heat transfer is limited due to radiation, convection, and thermal conductivity. Reducing sweat formation limits heat loss through evaporation. The contraction of the muscles of the hair follicles leads to the appearance of "goose bumps". The occurrence of a subjective feeling of chills is directly related to a decrease in skin temperature and irritation of the skin cold thermoreceptors, the signal from which enters the hypothalamus (Figure 9.2).

Stage 2. The body temperature at this stage reaches a new level of the temperature setting point. Heat production and heat transfer are balanced and there is no further increase in temperature, thermoregulation occurs by mechanisms similar to normal. At the same time, the skin vessels expand, the pallor disappears, the skin becomes hot to the touch, and the shivering and chills disappear. The person at the same time experiences a heat feeling.

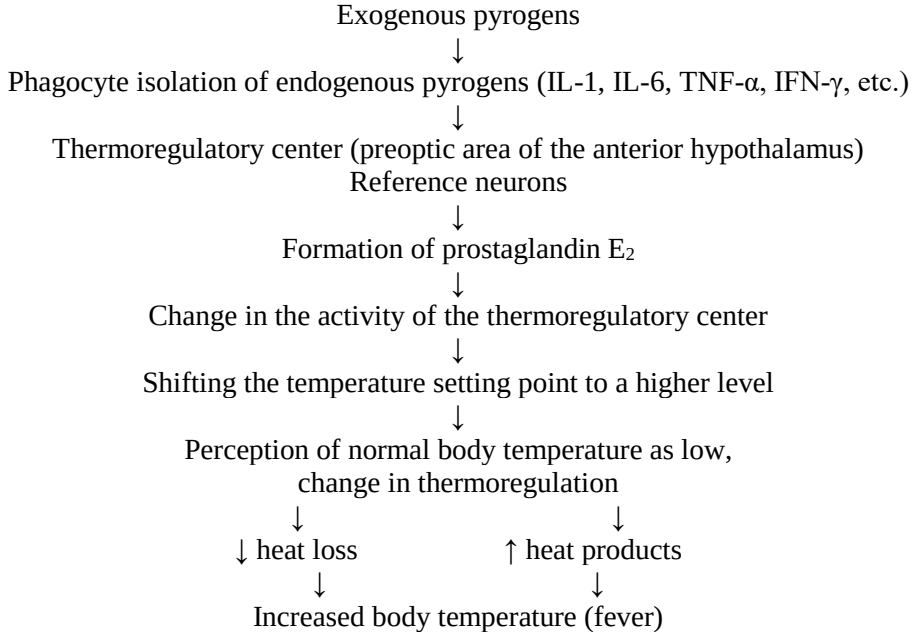

Figure 9.2 Scheme of the fever pathogenesis (stage 1)

Classification of fever

1. Depending on the degree of temperature increase:
- subfebrile (from 37.1 to 38°C);
- febrile-moderate (from 38.1 to 39°C);
- pyretic - high (39.1 to 41°C);
- hyperpyretic-excessive (above 41°C)

2. By the type of temperature curves:

The temperature curve is a graphical representation of the daily temperature variation. The type of temperature curve depends on the nature of the factor that caused the fever, as well as on the reactivity of the human body.

1. Constant fever (febris continua). The temperature is usually 38-39°C. During the day, the difference between the morning and evening temperature does not exceed 1°C. It is characteristic of croup pneumonia, stage II typhoid fever, erysipelas (Figure 9.3 A).

2. Laxative (remitting) fever (febris remittens). The temperature is high, the daily temperature fluctuations exceed 1-2°C, the morning minimum is above 37°C. It is characteristic of tuberculosis, purulent diseases, focal pneumonia, stage III typhoid fever, viral diseases, rheumatoid arthritis (Figure 9.3 B).

3. Intermittent fever (febris intermittens) is characterized by daily temperature fluctuations of more than 1-3°C. In the morning, the temperature is within normal limits. It is observed in malaria, Mediterranean fever (Figure 9.3 C).

4. Debilitating (hectic) fever (febris hectica) is characterized by large (3-4°C) daily temperature fluctuations, which alternate with its drop to normal and subnormal values. Such fluctuations in body temperature can occur several times a day, which is accompanied by a debilitating sweat. It is typical for severe pulmonary tuberculosis, sepsis (Figure 9.3 D).

5. Recurrent fever (febris recurrens) - characterized by alternating periods of high temperature (pyrexia) with non-sporadic periods (apyrexia) lasting 4-5 days. Characteristic of recurrent typhus (Figure 9.3 E).

6. Undulating fever (febris undulans). There are periodic gradual increases in temperature (for several days), and then a gradual decrease in the level to normal figures. Such" waves " follow one another for a long time. It is characteristic of brucellosis, lymphogranulomatosis (Figure 9.3 F).

Stage 3. A gradual decrease in temperature for 2-4 days with slight evening rises is called lytic. The sudden, rapid end of the fever with a drop in temperature to normal during the day is called critical. As a rule, a rapid drop in temperature is accompanied by a profuse sweat.

The stage of temperature reduction begins in connection with the removal of exogenous pyrogens and the cessation of the formation of endogenous pyrogens, their action on the thermoregulation center. The activity of the reference neurons is restored, the temperature setting point is lowered to the initial level before the fever. This leads to a change in thermoregulation: heat transfer exceeds heat production. There is an expansion of the skin vessels and the loss of excess heat by the body, excessive sweating, increased diuresis.

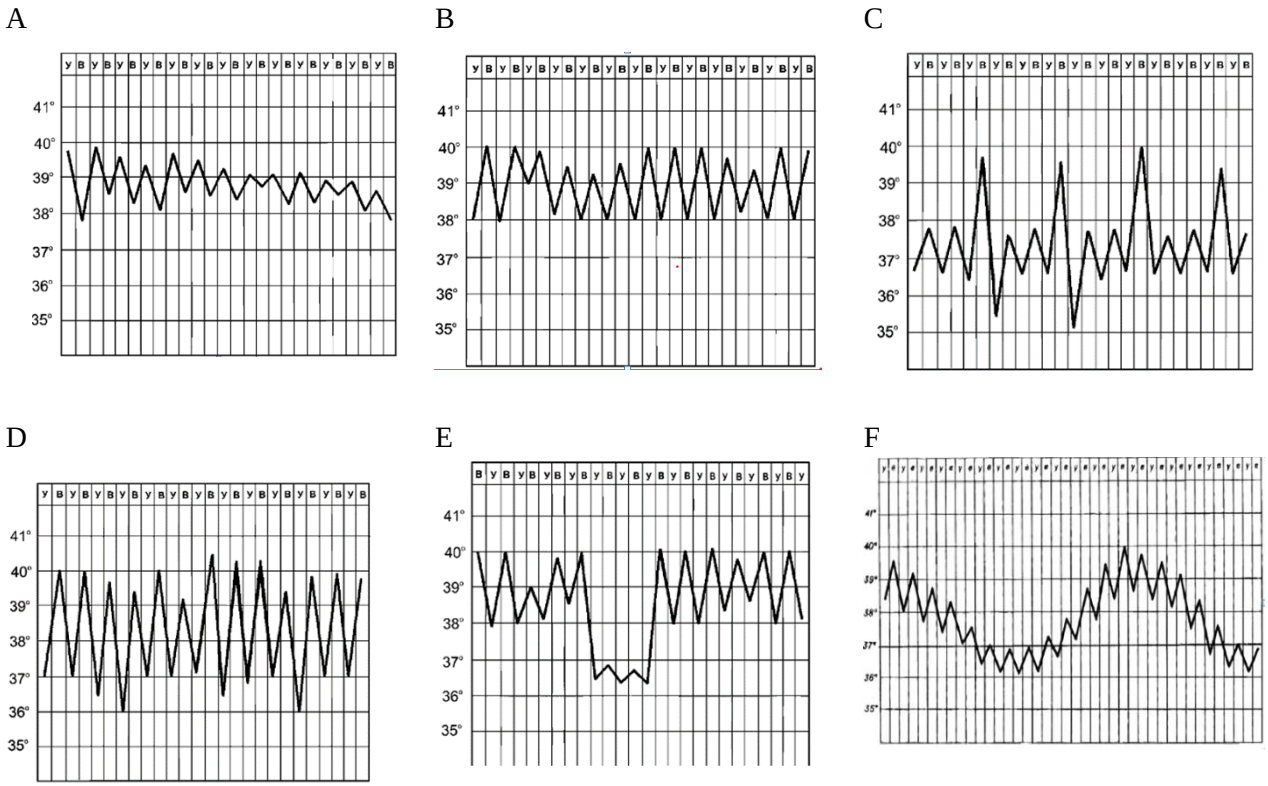

Figure 9.3 Types of temperature curves in fever. A. Persistent fever. B. Debilitating fever. C. Intermittent fever. D. Debilitating fever. E. Recurrent fever. F. Undulating fever.

Changes in the metabolism, function of organs and systems in fever

Changes in carbohydrate and fat metabolism are associated with the excitation of the sympathetic autonomic nervous system, accompanied by an increased breakdown of glycogen in the liver and increased lipolysis. This leads to an increase in blood glucose. Sometimes a febrile patient is found to have glucosuria. Increased mobilization of fat from the depot and its oxidation, which is the main source of energy in patients. Activation of proteolysis in the muscles, inhibition of protein synthesis due to the action of cortisol, reduced protein intake from food due to anorexia leads to a decrease in body weight with prolonged fever.

Fever may be accompanied by shifts in the acid-base balance. In febrile fever, gas alkalosis may develop (due to hypocapnia), and in pyretic fever, metabolic acidosis.

Catecholamines cause tachycardia. The indicators of the stroke and minute volume of the heart increase. Blood pressure may increase in the first stage of fever (because there is a spasm of the skin vessels), in the second stage it becomes normal or decreases by 10-15% compared to the norm (because the skin vessels expand). In the third stage of fever, blood pressure is reduced or normal. With a critical decrease in body temperature, acute vascular insufficiency (collapse) may develop. Possible violations of microcirculation in the lungs - stasis, stagnation. Breathing is somewhat shortened in the first stage of fever and is more frequent in the second stage, which contributes to an increase in heat transfer.

In the first stage of fever, diuresis increases. This is due to an increase in blood pressure due to spasm of the skin vessels and the influx of a significant mass of blood into the internal organs, including the kidneys. In the second stage of fever, diuresis is reduced, which is mainly due to the retention of water and sodium in the tissues (increased secretion of aldosterone) and increased evaporation of water from the surface of hyperemic skin and mucous membranes. In the third stage of fever, the diuresis increases again, and with a critical drop in temperature due to a sharp increase in sweating and hypotension, the diuresis decreases. Sometimes albuminuria develops, and hyaline cylinders appear in the urine.

Significant changes occur with fever in the gastrointestinal tract. The secretion of gastric, pancreatic and intestinal juices is suppressed. The motility of the stomach is suppressed and its emptying is inhibited, which causes vomiting. Intestinal peristalsis decreases, causing spastic or atonic constipation.

In the central nervous system, there is a separation of the processes of excitation and inhibition, so there may be insomnia, a feeling of exhaustion, fatigue, headache. Due to the immaturity of the central nervous system and the imperfection of the thermoregulation system, children under the age of five may develop seizures.

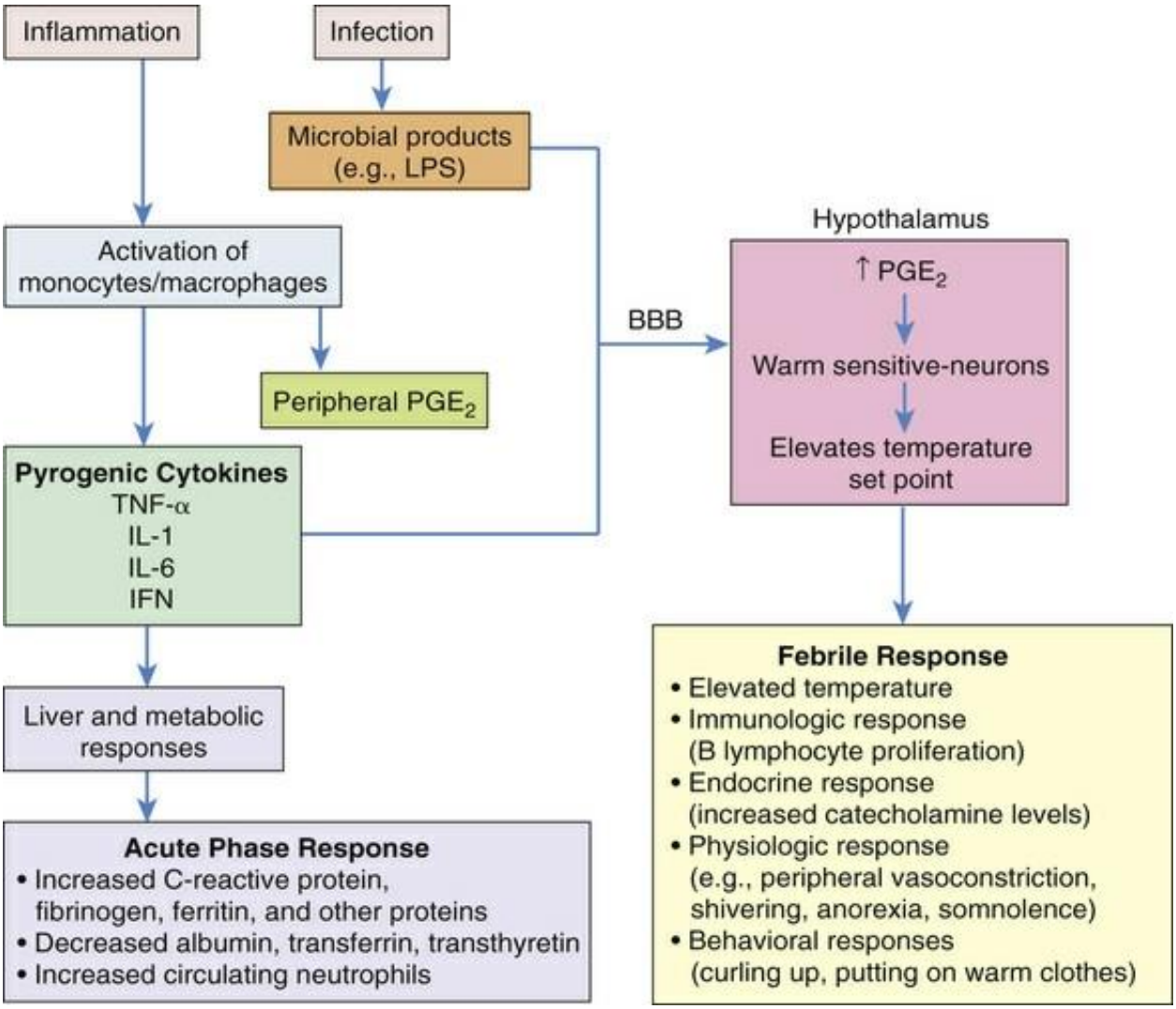

Figure 9.4 Pathogenesis of fever and acute phase response.
BBB, blood-brain barrier; IFN, interferon; IL-1, IL-6, interleukin-1, interleukin-6; LPS, lipopolysaccharide; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-alpha. (Adapted from Bennett JE et al: Mandell, Douglas, and Bennett's principles and practice of infectious disease, ed 8, Philadelphia, 2015, Saunders.)

Biological significance of fever

Adaptive value of fever:

- with fever, the immune response of the body increases due to the activation of T-and B-lymphocytes, the acceleration of the transformation of the latter into plasma cells, which stimulates the formation of antibodies, increases the formation of interferon.
- a moderate degree of rise in body temperature can activate the function of phagocytic cells and natural killer cells.
- enzymes that inhibit the reproduction of viruses are activated.
- reproduction slows down and the resistance of microorganisms to drugs decreases.
- the barrier and antitoxic functions of the liver are increased, which is realized due to hepatocytes that intensively produce acute phase proteins.
- an increase in body temperature with fever is often the first and only sign (alarm signal, trouble) of any disease.

Pathogenic significance of fever:

- direct damaging effect of high temperature on the body, the risk of hyperthermia;
- mediated effects of fever:
  - cardiovascular system: collapse, heart failure.

- gastrointestinal tract: loss of appetite, weight loss, dyspepsia.
- central nervous system: headache, drowsiness, apathy, delirium, hallucinations, convulsions in children.
- water-electrolyte metabolism: hyperhydration, risk of brain edema.

Characteristics of the acute phase response concept. Mediators of the acute phase response. Pathogenesis of manifestations.

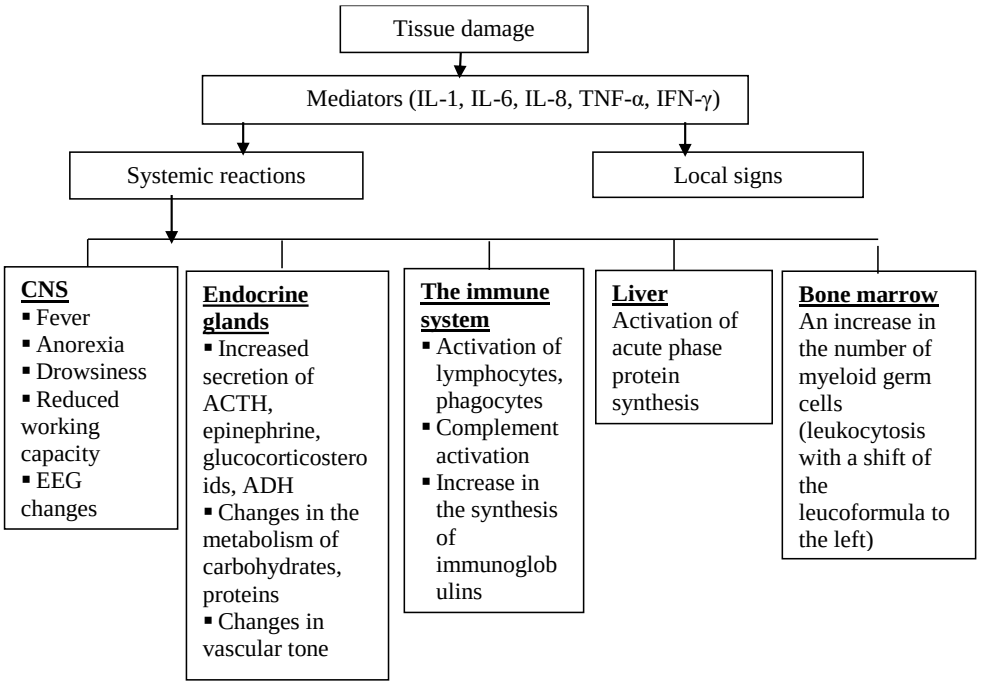

Figure 9.5 Pathogenesis of the acute phase response

The concept of pyrotherapy

Pyrotherapy is a method of treatment using artificial temperature increase to stimulate the mechanisms of innate and adaptive immunity and reparative processes in tissues.

The creation of artificial hyperthermia is carried out:

1. Introduction of pathogens of infectious diseases (malaria, recurrent typhus, etc.) and vaccines into the body.
2. The introduction of pyrogenic substances-foreign proteins (horse serum, blood of another group, etc.), pyrogenal.
3. Using heated air, water.
4. Exposure to electric and magnetic fields of high and ultra-high frequency (electropyrexia, inductopyrexia).

Systemic pyrotherapy is performed by raising the body temperature with purified exopyrogens (pyrogenal). An increase in body temperature stimulates adaptive processes in the body: specific and non-specific mechanisms of reactivity (used for syphilis, gonorrhea, post-infectious arthritis), plastic and reparative processes in bones, tissues and parenchymal organs (used for their damage, dystrophy, after surgical interventions).

Local pyrotherapy is used to stimulate regional defense mechanisms (immune and non-immune), repair, and blood circulation. Regional pyrotherapy is used in the treatment of skin diseases (eczema, psoriasis), some malignant neoplasms. The antitumor effects of pyrotherapy include inhibition of mitosis (especially in the S-phase) of the tumor cell, denaturation of proteins, lipoproteins and many enzymes, which is combined with their hyperhydration and destruction, an increase in the tumor tissue of glutathione, which damages the DNA of tumor cells, an increase in blood viscosity and a violation of microhemocirculation in the tumor vessels, as a result, an increase in hypoxia, acidosis, hyperosmia, which reduce the viability of the tumor, cancer cells, as well as in increasing the effects of chemo-, radio - and immunotherapy.

Hyperthermia: definition, etiology, classification, pathogenesis. Differences between overheating and fever.

Hyperthermia is a typical pathological process that occurs in response to the action of high ambient temperature, is characterized by a violation of the thermoregulation process and is accompanied by an increase in body temperature above normal.

As a rule, hyperthermia is a reversible process and after the termination of the damaging factor, the human body temperature returns to normal values.

Etiology. The cause of hyperthermia is the high temperature of the environment (hot climate, work in industrial premises with high temperature, long stay in the bath, sauna). Conditions for the occurrence of hyperthermia: high humidity.

Pathogenesis of hyperthermia

The compensation stage begins with the effect of the heat factor on the body, which leads to irritation of the skin and internal organs thermal thermoreceptors, a subjective feeling of increased temperature and behavioral reactions are formed. In case of impossibility or ineffectiveness of behavioral reactions, the maintenance of the body's temperature balance in the compensation stage occurs due to the activation of heat transfer processes (radiation, convection and evaporation from the skin surface). There is a reflex expansion of the vessels of the skin, anastomoses open between the arterioles and venules, blood enters the capillaries, blood filling of the vessels of the skin increases. More blood flows to the periphery from the internal organs, whose temperature is higher, and heat transfer by radiation and convection increases significantly. Heat transfer by evaporation occurs with the participation of sweat glands. The more blood flows to the sweat glands, the more intense the evaporation processes and the more efficient the heat transfer. In response to the action of mediators of the sympathetic nervous system, there is an increase in the frequency of respiratory movements, while the evaporation of moisture from the surface of the alveoli increases, heat transfer increases ("thermal dyspnea" is formed).

In **the decompensation stage**, the mechanisms of thermoregulation are disrupted, the heat balance is disturbed, and the body temperature increases above normal values. The reason for the transition to the stage of decompensation is the long-term effect of the etiological factor and the depletion of the compensatory capabilities of the body. This stage is characterized by dehydration, disruption of the physiological systems and the development of irreversible changes in the cells as a result of the damaging effect of high temperature.

Dehydration leads to an increase in blood viscosity and disruption of blood supply to organs and tissues. As a result, tissue hypoxia develops. Under conditions of elevated body temperature, the activity of enzymes in the cells changes and the normal course of metabolic processes is disrupted. The blood accumulates metabolic products, under-oxidized compounds, and cell breakdown products, which leads to the development of metabolic acidosis and disorders in the body's life support systems.

Adrenal insufficiency, a decrease in the level of catecholamines in the blood causes a disorder of the cardiovascular system, a decrease in blood pressure. Due to acidosis, the respiratory center is irritated and the ventilation of the lungs increases. This contributes to the removal of large amounts of carbon dioxide and the development of gas alkalosis. Depression of the central nervous system function is associated with the development of hypoxia in the cells of the vital centers of the brain. Violations in the center of thermoregulation, vasomotor and respiratory centers lead to a disorder of the regulation of the vital activity of the body and aggravate the course of hyperthermia.

The stage of decompensation is manifested by a deterioration in the general condition of a person: there is a strong feeling of heat and thirst, dryness of the mucous membranes and skin due to sweating disorders, severe headache, changes in consciousness, nausea or vomiting, decreased heart rate and blood pressure. If the effect of the etiological factor does not stop, then **a hyperthermic coma** develops. This condition is characterized by loss of consciousness, convulsions, and multiple organ failure.

Heat stroke is a special form of hyperthermia that occurs as a result of a decrease in the efficiency of heat transfer mechanisms in conditions of high ambient temperature and is accompanied by a rapid increase in body temperature.

The cause of heat stroke is the combined effect of high ambient temperature and high humidity. A feature of the development of heat stroke is the rapid course and increase in body temperature to high values.

The compensation stage in the pathogenesis of heat stroke is not expressed. It proceeds very quickly, often without clinical manifestations. Compensatory processes, as a rule, are ineffective, since convection and sweating are impossible, there is a rapid breakdown of compensation mechanisms.

At **the stage of decompensation**, the main physical and chemical constants of the body change in the body, which leads to a violation of the normal course of metabolic processes in cells: the process of protein breakdown (proteolysis) is activated, the content of ammonia in the blood increases, under-oxidized compounds accumulate, cell breakdown products and toxemia develops. A violation of cardiovascular activity in the decompensation stage is associated with an increase in the load on the heart, an increase in blood viscosity and the damaging effect of high temperature. This leads to acute heart failure and disruption of adequate blood supply to organs and tissues. Blood pressure decreases, and perfusion of the lungs, kidneys, and other organs is disrupted. Multiple organ failure develops.

Sunstroke - a special form of hyperthermia, which is characterized by an increase in body temperature as a result of direct exposure to sunlight

Sunstroke develops when the surface of the skin and deep tissues of the body are heated by radiation heat - the infrared part of solar radiation, which is able to warm up not only the surface, but also the deep tissues of the body. The main link in the pathogenesis is a violation of blood circulation in the brain. There is an expansion of blood vessels, which contributes to an increase in blood flow to the tissues and the development of brain edema. Changes in the metabolism and sensitivity of neurons in the vasomotor and respiratory centers can lead to a violation of respiration and blood circulation, a decrease in the effectiveness of all compensatory mechanisms.

Differences between overheating and fever

Indications	**Overheating the body**	**Fever**
Etiology	High ambient temperature	Pyrogen
Thermoregulation function	Failure of thermoregulation (in the decompensation stage)	Active restructuring of the thermoregulation system
Thermal installation point	The temperature setting point does not shift	Shifting the temperature setting point to a new, higher level
Temperature maximum	43°C and higher	41-42 °C
What determines the degree of temperature increase	Physical conditions of the body's heat exchange with the environment	The offset level of the thermal installation point
Dependence on external conditions (air temperature, humidity, wind speed, etc.).	Yes	No
Chills	No	It is noted in the first stage
The effectiveness of taking antipyretic drugs	No	Yes
Significance for the body	Pathogenic	Adaptive and pathogenic

Table 9.1 Distinctive signs of overheating of the body and fever.

Hyperthermic reactions - a short-term increase in body temperature, not associated with the action of an external temperature factor. Hyperthermic reactions include heat trauma under stress, heat convulsions, etc.

Thermal stress injury occurs as a result of prolonged physical work (contractile thermogenesis) in conditions of high temperature and humidity (more than 60%). Most often, heat injury develops in athletes-long-distance runners at high ambient temperatures and / or with a violation of the hydration regime of the body.

The outcome of a heat injury may be **heat convulsions**. They occur during muscular work in conditions of overheating (stoker's cramps). The development of this condition is based on profuse sweating, in which a large amount of electrolytes (Na^+, Cl^-, Ca^{2+}, etc.) is lost and the contractile activity of skeletal muscles is disrupted. Heat convulsions are manifested by pain, spasm of the muscles of the extremities.

Hypothermia is a typical pathological process that occurs in response to the action of low ambient temperature, characterized by a violation of the body's heat balance and a decrease in body temperature below normal.

By localization, hypothermia is divided into local (local) and general (systemic).

Local hypothermia occurs when a low ambient temperature affects a local area of the body, for example, when frostbite occurs in the upper or lower extremities. Systemic hypothermia occurs with general hypothermia of the body and is associated with impaired blood circulation in organs and tissues.

Etiology. The cause of hypothermia is a low ambient temperature. Hypothermia of a person most often develops in the air temperature range from -10 to +10 °C. Conditions that contribute to the development of hypothermia include wind, high humidity, wet clothing, skeletal muscle pathology (paralysis), thyroid hormone deficiency, stress, and alcohol intoxication.

Pathogenesis of hypothermia

The compensation stage begins with the receipt of signals from the skin's thermoreceptors to the hypothalamic thermoregulation center. Low ambient temperature is perceived by cold receptors. Initially, behavioral reactions are formed, the main purpose of which is to reduce the impact of adverse environmental temperature conditions. If the behavioral reactions are ineffective and the effect of the etiological factor continues, the body temperature of the person decreases. Heat is generated by activating contractile and non-contractile thermogenesis. There is an increase in heart rate and an increase in blood pressure, an increase in the frequency of respiratory movements, and a decrease in diuresis.

Manifestations of the compensation stage: pallor or cyanosis of the skin, "goose" skin, chills, decreased sweating.

The decompensation stage is characterized by a violation of the body's heat balance, a decrease in body temperature below normal and a breakdown of thermoregulation mechanisms. In conditions of low body temperature, the activity of cellular enzymes decreases and metabolic processes slowdown, which leads to a decrease in the efficiency of heat production and the inability to maintain heat balance. The central nervous system is dominated by the processes of inhibition, the activity of vital centers in the medulla oblongata - vasomotor and respiratory-is disrupted. As a result, the heart rate and respiratory movements are reduced. The higher nervous activity is suppressed, and hypothermic sleep occurs. The risk of death in this case increases. With a further decrease in body temperature, the functioning of the vasomotor and respiratory centers stops, there is a stop of breathing and cardiac activity, and the death of the body occurs.

Manifestations of the decompensation stage: lack of trembling, lethargy, impaired consciousness with the development of coma, decreased pain sensitivity.

The use of artificial hypothermia in medicine

Artificial reduction of body temperature (hibernation) is widely used in medicine.

Medical hibernation is a method of controlled lowering of the temperature of the body or its organs in order to reduce the intensity of metabolism, increase their resistance to hypoxia.

With deep cooling of the body, metabolic processes are inhibited, and the need for oxygen in the tissues decreases. This feature of oxygen metabolism, in particular the brain, is taken into account by surgeons during operations in conditions of a significant decrease or even temporary cessation of blood circulation: operations on " dry " organs (heart, brain, other organs). Usually, they focus on the temperature in the rectum in the range of 28-30° C, but if necessary, you can create a deeper hypothermia using artificial blood circulation, muscle relaxants, metabolic inhibitors and other manipulations. For general cooling of the body, liquids with a temperature of +2 to -12° C are used, circulating in special "cold" suits worn on the patient, or "cold" blankets, with which they are covered.

In a number of cases, local hypothermia is used, for example, of the head, with the help of a special helmet put on the patient's head, permeated with tubes-thermodes, through which the cooling liquid circulates. Locally controlled hypothermia of individual organs and tissues (brain, kidneys, stomach, liver, prostate) is used when it is necessary to perform surgical interventions or other therapeutic manipulations on them.

In order to eliminate or reduce the pronounced adaptive reactions of the body in response to hypothermia, to limit the stress response, the patient is given anesthesia and injected with muscle relaxants and neuroplegic substances (lytic cocktail) before cooling. Together, these manipulations provide a gradual decrease in total and cellular metabolism, the consumption of oxygen by cells, the release of carbon dioxide and other metabolites, and prevent violations of the acid-base balance, the imbalance of ions and water in the tissues.

The advantages of medical hibernation are that there are no vital violations of the functions of the cerebral cortex and reflex activity of the nervous system, reduced excitability, conductivity and limited automatism of the cells-drivers of the rhythm of the conducting system of the heart, sinus bradycardia is formed, the minute and stroke volumes of the heart fall, arterial blood pressure decreases, functional activity and the level of metabolism in the organs and tissues of the body is inhibited.

Practical lesson 10. Hypoxia. Hyperoxia.

Key questions of the session:

1. Hypoxia. Definition of the concept. Classification. Mechanisms of hypoxic necrobiosis.
2. Hypoxic hypoxia: types, etiology, pathogenesis. Mountain sickness, altitude sickness.
3. Etiology and pathogenesis of hemic and circulatory hypoxia.
4. Etiology and pathogenesis of histotoxic hypoxia.
5. Hyperoxia as a cause of hypoxia. Hyperoxygenation, therapeutic and pathological effects.
6. Urgent and long-term mechanisms of compensation for hypoxia.

Indicators of oxygen supply to the body are normal

- pO_2 (partial pressure of oxygen) is the partial pressure of oxygen in the blood. The partial pressure of oxygen in arterial blood is 85-100 mm Hg., the partial pressure of oxygen in the venous blood is 40 mm Hg. and more.

- the oxygen capacity of the blood is the maximum amount of oxygen that can be associated with 100 ml of blood when it is fully saturated with oxygen (calculated value). The oxygen capacity of arterial blood is 21 vol.% (Vol.%).

- the volumetric oxygen content in the blood is the actual oxygen content in the blood of a person under specific conditions. The volumetric oxygen content in arterial blood in a healthy person is 19 vol%, the volumetric oxygen content in venous blood in a healthy person is 14 vol%, and the arteriovenous oxygen difference is 5 vol%.

- saturation (saturation of hemoglobin with oxygen) is the ratio of the volumetric oxygen content in the blood to the oxygen capacity of the blood. Saturation is normal 96-98%.

- pCO_2 (partial pressure of carbon dioxide) is the partial pressure of carbon dioxide in the blood. The partial pressure of carbon dioxide in the arterial blood in a healthy person is 35-45 mm Hg. Art., in the venous blood, the partial pressure of carbon dioxide is 45-48 mm Hg. Art.

- pH (hydrogen ion exponent) - negative decimal logarithm of the concentration of hydrogen ions, pH of arterial blood in a healthy person 7.35-7.45.

Hypoxia. Definition of the concept. Classification. Mechanisms of hypoxic necrobiosis

Hypoxia is a typical pathological process that occurs when there is an insufficient supply of oxygen to the tissues and cells of the body or a violation of the use of oxygen in the processes of biological oxidation. Causes of oxygen deficiency in Figure 10.1.

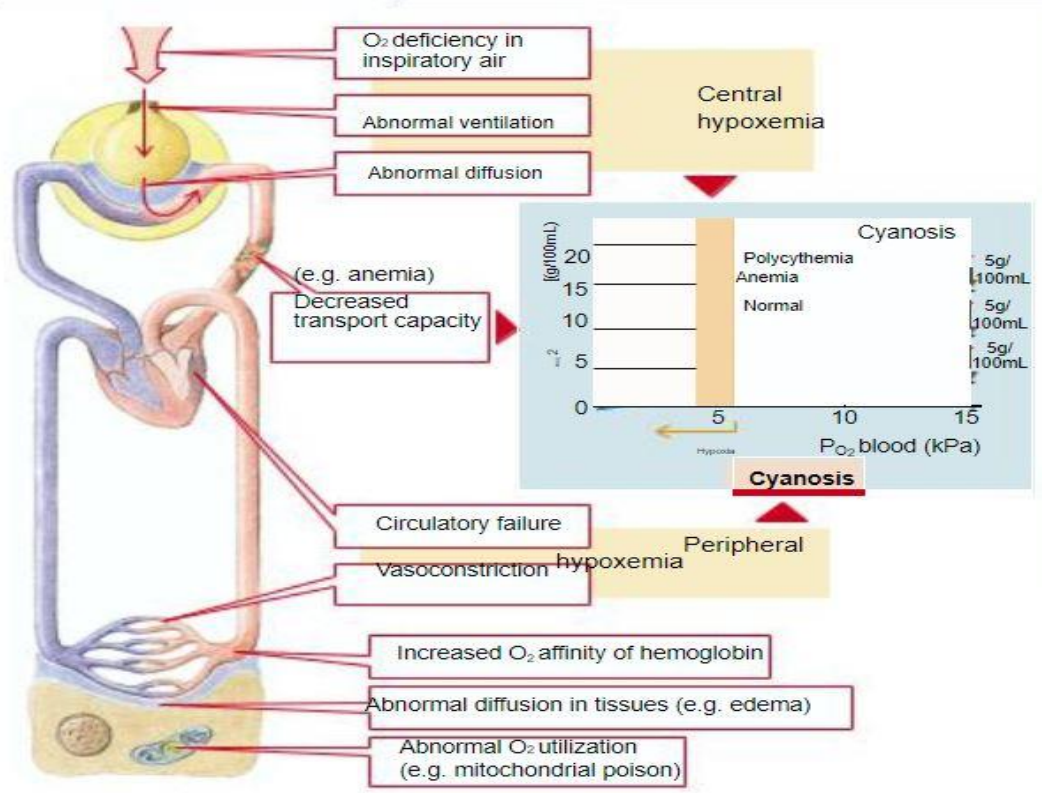

Figure 10.1 Causes of oxygen deficiency (Silbernagl S., Lang F. Color Atlas of Pathophysiology. – 2015. – P.91)

Hypoxemia is a decrease in the partial pressure of oxygen in the blood, hypoxemia can be arterial and venous

Classification of hypoxia

By pathogenesis:

1. Hypoxic hypoxia

- normobaric (at normal atmospheric pressure due to a decrease in the partial pressure of oxygen or an increase in the partial pressure of carbon dioxide in the inhaled air
- hypobaric (at reduced atmospheric pressure)
- respiratory (due to respiratory disorders)

2. Hemic hypoxia

- anemic type
- as a result of inactivation of hemoglobin

3. Circulatory hypoxia

- local (local)
- systemic

4. Tissue hypoxia (histotoxic)

5. Hypoxia with hyperoxia

Hypermetabolic hypoxia, or load hypoxia, is also distinguished - an increase in the rate of oxygen consumption and the formation of carbon dioxide by cellular and tissue structures, exceeding their ability to provide the body with oxygen and eliminate carbon dioxide, for example, with excessive functional load, including with excessive muscle activity.

According to the speed of process, hypoxia can be:

- the most acute (for example, with arterial bleeding);
- acute (for example, with venous bleeding);
- subacute (for example, with nitrite poisoning);
- chronic (for example, with chronic heart failure).

In terms of severity, hypoxia can be:

- hidden (detected only under load);
- compensated (oxygen content in tissues is normal, due to the tension of oxygen delivery systems);
- decompensated (oxygen content in tissues is reduced);
- terminal - irreversible.

The general pathogenesis of hypoxia is shown in the Figure 10.2.

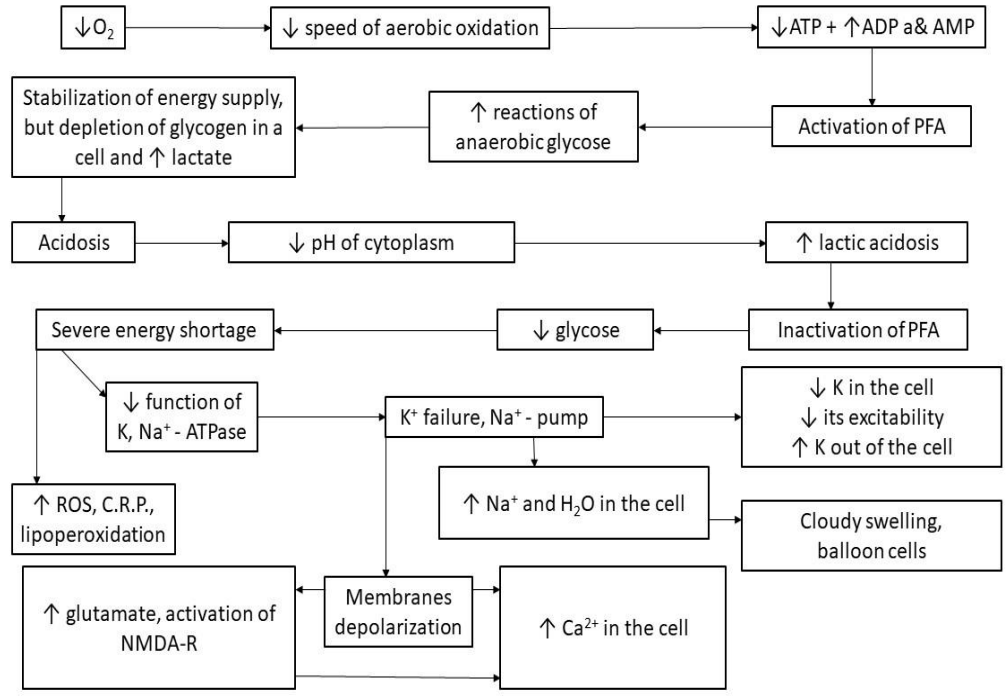

Figure 10.2 The general pathogenesis of hypoxia (Tsygan V. Pathophysiology. Clinical pathophysiology. – 2018. – P. 286)

Hypoxic hypoxia: types, etiology, pathogenesis. Mountain sickness, altitude sickness

Hypoxic hypoxia occurs with a decrease in pO_2 in the inhaled air (exogenous type) or with impaired function of the external respiration system (endogenous type). Depending on the change in the level of barometric (atmospheric) pressure, hypoxic hypoxia can be hypobaric and normobaric.

Hypobaric hypoxic hypoxia occurs when climbing to a height (altitude sickness, mountain sickness). Altitude sickness develops during a rapid ascent to an altitude above 2000 m in the mountains or when flying in aircraft that are not equipped with a pressurized cabin. Altitude sickness is manifested by general malaise, dizziness, drowsiness. If the person stays at this altitude or rises higher, the symptoms worsen. Altitude sickness occurs as a result of a drop in barometric pressure, and as a result of a drop in the partial pressure of oxygen in the inhaled air.

Altitude sickness is a type of altitude sickness. In addition to reducing the partial pressure of oxygen, other factors are also important: physical fatigue, cooling, dehydration, ultraviolet radiation, and severe weather conditions. With a decrease in pO_2 in the inhaled air, the pO2 in the arterial blood decreases, the saturation of hemoglobin with oxygen and the total oxygen content in the blood decrease, that is, arterial hypoxemia develops. Arterial hypoxemia is the main link in the pathogenesis of hypoxic hypoxia.

Normobaric type of hypoxic hypoxia develops when a large number of people are in poorly ventilated rooms, which is accompanied by a decrease in the oxygen content in the inhaled air, and, as a consequence, in the alveolar air and in the blood.

Hypoxic hypoxia also develops under the influence of endogenous causes associated with the pathology of the respiratory system (respiratory type). Respiratory type of hypoxic hypoxia occurs in any pathology of the external respiratory system: in violation of ventilation processes of the alveoli, in violation of diffusion of gases through the alveolar-capillary barrier and in violation of ventilation-perfusion relations. Hypoventilation of the alveoli develops in violation of the airway patency, a decrease in the respiratory surface of the lungs (pulmonary edema, pneumonia), a decrease in lung expansion (pneumothorax, exudate in the pleural cavity), a decrease in the mobility of the osteochondral apparatus of the chest, paralysis of the respiratory muscles (myasthenia gravis, curare poisoning, tetanus), disorders of the central regulation of respiration. Disturbance of oxygen diffusion through the alveolar-capillary membrane occurs when it thickens: pneumonia, pulmonary edema. Violation of the ventilation-perfusion relationship is associated with impaired blood flow in the pulmonary artery system, for example, thrombosis, stenosis of the pulmonary artery vessels. As a result of all these reasons, the saturation of hemoglobin and pO_2 in arterial blood is significantly reduced. Thus, arterial hypoxemia develops. Disturbances of the external respiration system are also accompanied by a violation of the elimination of carbon dioxide from the body, that is, it occurs when hypercapnia is combined.

With exogenous hypoxic hypoxia, the following changes in indicators are noted:

- the partial pressure of oxygen in arterial blood decreases (arterial hypoxemia);
- the partial pressure of carbon dioxide in arterial blood is reduced (arterial hypocapnia)
- the volumetric oxygen content in arterial blood decreases;
- the volumetric oxygen content in venous blood decreases;
- arterio-venous oxygen difference, as a rule, does not change;
- saturation decreases
- the pH value of the blood rises (gas alkalosis).

In respiratory (endogenous) hypoxic hypoxia, the following changes in indicators are noted:

- the partial pressure of oxygen in arterial and venous blood decreases (arterial and venous hypoxemia);
- the partial pressure of carbon dioxide in arterial blood, as a rule, is increased (arterial hypercapnia)
- the volumetric oxygen content in arterial blood decreases;
- the volumetric oxygen content in venous blood decreases;
- arterio-venous oxygen difference, as a rule, does not change;
- saturation decreases
- the pH value of the blood decreases (gas, and then mixed acidosis).

Etiology and pathogenesis of hemic and circulatory hypoxia

The hemic type of hypoxia develops with a decrease in the oxygen capacity of the blood, which is associated with a deficiency in the number of circulating erythrocytes, a decrease in the concentration of hemoglobin (anemic type) or a decrease in the oxygen-binding properties of hemoglobin (inactivation type). Anemic type of hemic hypoxia occurs in acute and chronic blood loss, in violation of hematopoiesis in the red bone marrow, with increased hemolysis. The inactivation type of hemic hypoxia occurs when pathological forms of hemoglobin appear: methemoglobin, carboxyhemoglobin, etc.

Methemoglobin is a compound of hemoglobin in which iron has an oxidation state of 3+. Normally, the content of methemoglobin in the blood ranges from 1% to 3%. The increase in the content of methemoglobin in

the blood is hereditary or more often acquired in nature. Methemoglobin-formers are aniline dyes, nitrates, nitrites, some drugs (lidocaine, procaine). The severity of clinical manifestations in the formation of methemoglobin depends on its concentration in the blood. With a methemoglobin content of 3-15%, slight changes in skin color are noted (pale, gray); 15-20% of methemoglobin is cyanosis; 25-50% methemoglobin - general weakness, headache, dizziness, fainting, confusion, tachycardia, shortness of breath; 50-70% of methemoglobin - arrhythmia; changes in mental state, delirium, convulsions, coma; more than 70% of methemoglobin is fatal. Blood containing methemoglobin turns reddish brown.

Carboxyhemoglobin is a compound of hemoglobin with carbon monoxide (II) (CO, carbon monoxide). CO is a product of incomplete combustion, is formed during fires, is contained in the exhaust gases of automobile internal combustion engines, and tobacco smoke. Carbon monoxide has a high (300 times) affinity for hemoglobin, therefore, even small concentrations of carbon monoxide in the inhaled air lead to the formation of carboxyhemoglobin. In addition, carboxyhemoglobin is a strong compound and does not dissociate well. The presence of carboxyhemoglobin in the blood gives the blood a crimson hue. Methemoglobin and carboxyhemoglobin lose their ability to transport oxygen, which leads to a decrease in the oxygen capacity of the blood and the development of hypoxia.

With hemic hypoxia, the following changes in indicators are noted:

- the partial pressure of oxygen (pO2) in arterial blood is normal;
- the partial pressure of oxygen in the venous blood decreases (venous hypoxemia);
- the volumetric oxygen content in arterial blood decreases;
- the volumetric oxygen content in venous blood decreases;
- arterio-venous oxygen difference decreases;
- saturation decreases.

The circulatory type of hypoxia occurs with local and general circulatory disorders. In circulatory hypoxia, two forms are distinguished: local (local) and systemic. The etiological factors of local circulatory hypoxia are local circulatory disorders: thrombosis and embolism of the arteries, for example, in atherosclerosis; spasm of arteries, vasculitis, compression of arteries. Etiological factors of systemic circulatory hypoxia are violations of myocardial contractility (heart failure), a decrease in circulating blood volume (hypovolemia) due to the volume of circulating plasma (extensive burns, fluid loss through the gastrointestinal tract with diarrhea, with prolonged sweating), generalized decrease in vascular tone (adrenal insufficiency).

With circulatory hypoxia, the following changes in indicators are noted:

- partial pressure of oxygen (pO_2) in arterial blood is normal
- the partial pressure of oxygen (pO_2) in the venous blood is reduced (venous hypoxemia);
- volumetric oxygen content in arterial blood is normal;
- the volumetric oxygen content in venous blood is reduced
- arterio-venous oxygen difference increases;
- saturation decreases;
- blood pH value is reduced, non-gaseous acidosis.

Etiology and pathogenesis of histotoxic hypoxia

Histotoxic hypoxia (cytotoxic, tissue hypoxia) develops when the ability of cells to use oxygen for biological oxidation is impaired or when the processes of biological oxidation and phosphorylation are uncoupled.

A decrease in the ability of cells to use oxygen for biological oxidation is the result of inhibition of the respiratory enzyme chain, disruption of the synthesis of respiratory enzymes involved in biological oxidation; destruction of mitochondrial membranes, uncoupling of the processes of biological oxidation and phosphorylation. Inhibition of the chain of respiratory enzymes occurs in three main ways: persistent specific binding of active centers of respiratory enzymes by toxic compounds (cyanides, sulfide ions); nonspecific binding of functional groups of the protein part of the enzyme molecule by heavy metal ions; competitive inhibition as a result of blockade of the active center of the enzyme by a "pseudosubstrate". Violation of the synthesis of respiratory enzymes is associated with hypovitaminosis, deficiency of B vitamins - thiamine, niacin. The destruction of mitochondrial membranes occurs when lipid peroxidation processes are activated and reactive oxygen species are formed. Free radical oxidation of membrane phospholipids is especially intense after restoration of blood flow in previously ischemic areas of a tissue or organ.

A decrease in the efficiency of capturing by a cell of free energy released during aerobic biological oxidation is the result of a decrease in the conjugation of oxidation and phosphorylation on the respiratory chain of enzymes in mitochondria. In this case, the oxygen consumption by the cell increases, and the accumulation of free energy in the form of high-energy bonds decreases, and a significant part of the energy is dissipated in the form of heat. Intracellular acidosis, an excess of ionized calcium in the cell, non-esterified fatty acids, an excessive effect of adrenaline and thyroid hormones on the cell are disconnected from the processes of biological oxidation

and phosphorylation. Exogenous uncouplers of biological oxidation and phosphorylation are 2,4-dinitrophenol, dicumarin, gramicidin. As a result of a violation of the processes of oxygen utilization by the cell, its content in the venous blood increases, which leads to a decrease in the arterio-venous oxygen difference. In the histotoxic form of hypoxia, the arteriovenous oxygen difference is practically zero.

With histotoxic hypoxia, the following changes in indicators are noted:

- partial pressure of oxygen (pO2) in arterial blood is normal
- the partial pressure of oxygen (pO2) in the venous blood is increased;
- volumetric oxygen content in arterial blood is normal,
- the volumetric oxygen content in the venous blood is increased;
- arterio-venous oxygen difference decreases;
- saturation in arterial blood is normal;
- Saturation in venous blood is increased
- the pH value is reduced (non-gaseous acidosis).

Thus, with all forms of hypoxia in the mitochondria of cells, tissues and organs of the body, the formation of macroergs is reduced. A decrease in the formation and content of adenosine triphosphate in cells disrupts the functioning of cells and leads to damage to various structures. First of all, the work of Na-K-adenosine triphosphate-ase and Ca-adenosine triphosphate-ase is disrupted. Cells begin to lose potassium ions, sodium and calcium ions accumulate in them, intracellular acidosis develops due to the activation of anaerobic glycolysis processes. One of the first morphological signs of hypoxic cell damage is cytoplasm opacity. The neurons of the cerebral cortex are the most sensitive to hypoxia; the cells of bone tissue are the least sensitive to hypoxia.

Hyperoxia as a cause of hypoxia. Hyperoxygenation, therapeutic and pathological effects

Hypoxia with hyperoxia does not occur naturally and is the result of an artificial increase in the oxygen content in the inhaled air. With hyperoxia, the oxygen content in the blood increases due to its dissolution in the plasma. Hyperbaric oxygenation is used more often. Hyperbaric oxygenation is the inhalation of oxygen under high pressure for therapeutic purposes. Inhalation of oxygen under pressure leads to an additional dissolution of oxygen in the blood plasma, therefore, most tissues can satisfy their need for oxygen due to its physically dissolved fraction. Hyperbaric oxygenation is used for carbon monoxide poisoning, crash syndrome, severe anemia, air embolism, heart failure, complications of diabetes mellitus and is carried out in special pressure chambers.

Along with the therapeutic effect, hyperbaric oxygenation can be accompanied by a damaging effect. An increase in oxygen pressure in the inhaled air (oxygen poisoning) can be accompanied by the development of convulsive syndrome and pneumonia. An excess of oxygen leads to the activation of lipid peroxidation processes, which leads to damage to mitochondrial membranes. Damaged mitochondria are unable to utilize oxygen, which is accompanied by ATP deficiency and the development of tissue hypoxia.

Urgent and long-term mechanisms of compensation for hypoxia

Compensation mechanisms for hypoxia are subdivided into urgent and long-term.

Urgent mechanisms of compensation during hypoxia are associated with an increase in the function of an organ or tissue. Urgent mechanisms of compensation during hypoxia are: an increase in the frequency and depth of breathing, an increase in the number of functioning alveoli, an increase in heart rate and myocardial contractility, changes in the microvasculature, including the opening and functioning of all microvessels. One of the compensation mechanisms during hypoxia is an increase in the oxygen capacity of the blood. An urgent mechanism for increasing the oxygen capacity of the blood is the release of blood from the depot and the improvement of the dissociation of oxyhemoglobin in the tissues. An urgent cellular compensation mechanism during hypoxia is an increase in the efficiency of biological oxidation, which is associated with an increase in the activity of respiratory enzymes in mitochondria and activation of glycolysis.

Long-term mechanisms of compensation during hypoxia are associated with an increase in the mass / volume of an organ or tissue. Long-term mechanisms of compensation in hypoxia are: an increase in the number of alveoli and capillaries in the lungs, hypertrophy of the respiratory muscles and myocardium, neoangiogenesis. The long-term mechanism of an increase in the oxygen capacity of blood during hypoxia is an increase in the number of erythrocytes in the peripheral blood as a result of an increase in the processes of erythropoiesis in the bone marrow. Long-term mechanisms of compensation in the cell for development during hypoxia are an increase in the number of mitochondria and an increase in the amount of enzymes of the mitochondrial respiratory chain.

Practical lesson 11. Pathophysiology of metabolism. Violations of the acid-base balance (ABB)

Key questions of the lesson

1. The concept of the acid-base balance: the definition, the role in the body, the regulation mechanisms, the main indicators.
2. Acidosis. Classification, etiology, compensation mechanisms, clinical and laboratory manifestations.
3. Alkaloses. Classification, etiology, compensation mechanisms, clinical and laboratory manifestations.

The concept of the acid-base balance: the definition, the role in the body, the regulation mechanisms, the main indicators.

Acid-base balance (ABB) - the relative constancy of the hydrogen ions [H^+] concentration in the body's liquid media (blood, lymph, tissue fluid, intracellular fluid), due to the combined action of the buffer and some physiological systems of the body.

ABB is the most important body homeostatic parameter, the degree of saturation of hemoglobin with oxygen, the rate of oxygen return in the tissues of the body, the activity of enzymes and metabolism in the cells of the body, the rate of transmission of nerve impulses, etc. depend on the value of ABB.

The main indicator that characterizes the ABB is the pH-hydrogen index. pH is the negative decimal logarithm of the concentration of free hydrogen ions in the solution, i.e. **pH** = - lg [H^+]. The blood pH is one of the most rigid physiological constants of the body. Normally, the pH value varies slightly: the arterial blood pH is 7.35-7.45; the venous blood pH is 7.32-7.39, the pH inside the cells is variable. A decrease in the pH in the blood by 0.1 beyond the normal limits leads to a violation of breathing, the cardiovascular system activity. A decrease in pH by 0.3 causes an acidotic coma, and by 0.4 is incompatible with life. Therefore, a person has developed complex mechanisms for regulating changes in the ABB.

Mechanisms of ABB regulation

The rapid recovery of the acid-base balance is achieved by the buffer systems operation, and the constant maintenance of the blood pH is ensured by the removal of carbon dioxide by the lungs and the removal of some acids by the kidneys. A certain role in maintaining the acid-base balance belongs to the bone tissue, the gastrointestinal tract, and the liver (Figure 11.1).

A buffer is any system that tends to resist a change in pH when an acid or alkali is added to it

Solutions containing weakly dissociating acids, which are donators of hydrogen ions, and a salt of this acid with a strong base - an acceptor of hydrogen ions, have buffer properties. The buffer systems of the internal environment of the body are the bicarbonate buffer system, the phosphate buffer system, the protein buffer system, the hemoglobin buffer, and the ammonium buffer.

Bicarbonate buffer system - the ratio of carbonic acid (Figure 11.2) to its acid salt sodium bicarbonate - $\frac{H_2CO_3}{NaHCO_3}$. This ratio is a constant and is 1:20. Bicarbonate buffer is the main extracellular buffer, it accounts for more than 50% of the buffer capacity of the blood.

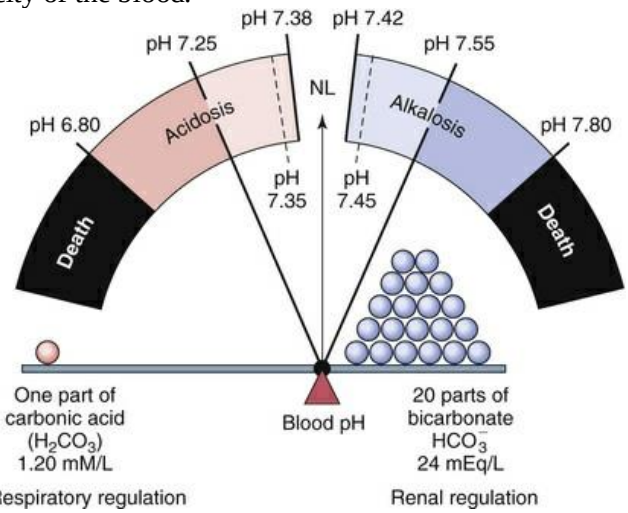

Figure 11.2 Ratio of Carbonic Acid and Bicarbonate Concentration in Maintaining pH Within Normal Limits. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

The phosphate buffer system - the ratio of monosubstituted sodium phosphate to diosubstituted sodium phosphate $\frac{NaH_2PO_4}{Na_2HPO_4}$. The ratio of acidic and basic components in the phosphate buffer is 1:4. The phosphate buffer plays a major role in maintaining the acid-base balance inside the cells and in the renal tubules.

Protein buffer system

Proteins are amphoteric, they simultaneously possess the properties of acids and bases. The protein buffer system of the blood is represented by blood proteins (albumin), in red blood cells there is a hemoglobin buffer.

The hemoglobin buffer consists of oxyhemoglobin and a reduced form of hemoglobin $\left(\frac{\text{oxyhemoglobin}}{\text{reduced hemoglobin}}\right)$. Oxyhemoglobin is a stronger acid than reduced hemoglobin.

The ammonium buffer consists of ammonia and an ammonium ion $\left(\frac{NH_3}{NH_4}\right)$. This buffer main component is ammonia, which is formed in the renal tubules epithelium and then secreted into the tubules' lumen.

The body's buffer systems react very quickly to changes in the hydrogen ions or hydroxyl ions concentration, but they can provide a short-term effect of normalizing the acid-base balance. Longer maintenance of the acid-base balance is provided by the activity of physiological systems, namely the respiratory system and the excretory system.

The respiratory system ensures the maintenance of the acid-base balance due to the excretion or retention of volatile acid in the body. In the human body, the volatile acid is carbonic acid. With the accumulation of carbonic acid in the body, the processes of ventilation of the alveoli increase and carbon dioxide is removed from the body. This process ensures the normalization of the acid-base balance within a few minutes.

The kidneys ensure the elimination of non-volatile acidic compounds from the body, such as uric acid, phosphoric acid, sulfuric acid, β-hydroxybutyric acid, acetoacetic acid, etc. These substances are formed in the body during the process of metabolism. The kidneys maintain the acid-base balance more slowly, for several hours or days, while the efficiency of the kidneys is higher. The kidneys provide regulation of the acid-base balance due to the following processes: acidogenesis (secretion of hydrogen ions into the urine); ammoniogenesis (formation of ammonia tubules in epithelial cells, followed by binding to hydrogen ions and the formation of ammonium ions); secretion or reabsorption of bicarbonates in the renal tubules. Therefore, the pH of the urine can vary quite significantly: from 4.5 to 8.0.

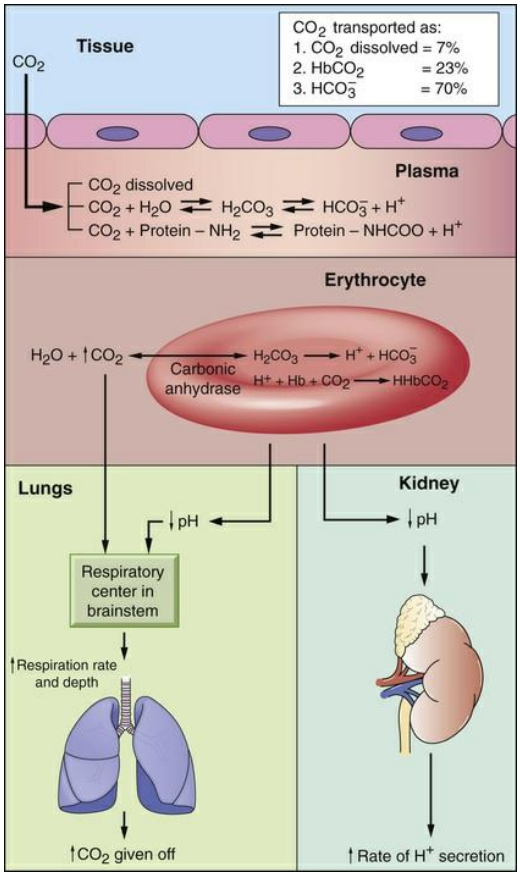

Figure 11.1 Integration of pH Control Mechanisms. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Indicators of acid-base balance

- actual (true) pH is the pH arterial blood value, determined without air access at 38^0 C. Normally, the pH of arterial and capillary blood is 7.35-7.45.

- the actual (true) partial pressure of carbon dioxide (pCO_2) is the value of CO_2 in arterial blood, determined without air access at a temperature of 38^0 C. In normal arterial blood pCO_2 35-45 mm Hg

-standard bicarbonate (SB) - the content of bicarbonates in the blood plasma at full oxygen saturation and at pCO_2 40 mm Hg, determined at 38^0 C. The normal SB is 22-26 mmol/l.

- actual (true) bicarbonate – (AB) - the concentration of true bicarbonates in the blood plasma. The norm is 22-25 mmol/l.

- excess (lack) of buffer bases (BE) - deviation of the concentration of the buffer bases of the plasma from the normal level. Normally 0, the permissible fluctuations are from +2.5 to -2.5 mmol/l.

Violations of the acid-base balance

In conditions of pathology, the acid-base balance may change (Figure 11.3). There are two groups of pathologies of the acid-base balance: acidosis and alkalosis.

By changing the pH value, **compensated** and **decompensated** forms of acidosis and alkalosis are distinguished. With compensated acidosis and alkalosis, the pH is within the normal range. In decompensated acidosis and alkalosis, the pH shifts beyond the normal range. For example, decompensated acidosis at a pH of 7.34 to 6.8; decompensated alkalosis at a pH of 7.46 to 7.8.

According to the mechanism of development of acidosis and alkalosis are divided into gas and non-gas.

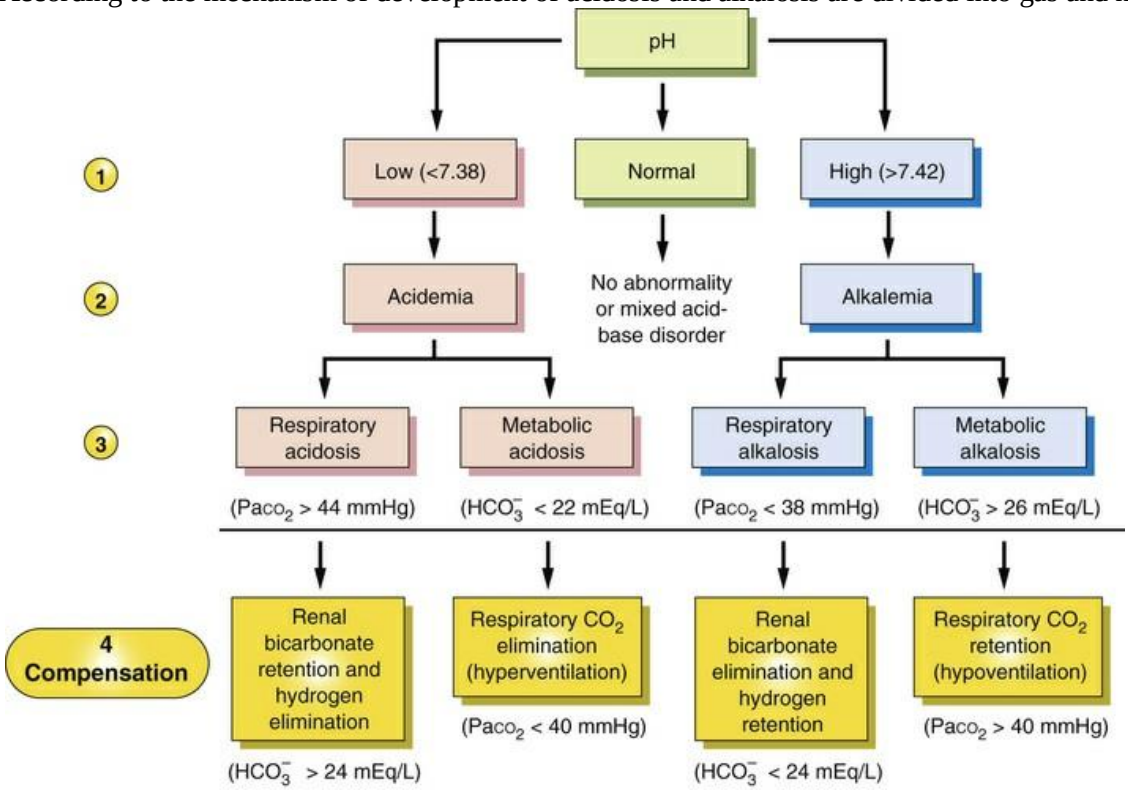

Figure 11.3 Primary and Compensatory Acid-Base Changes. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Acidosis. Classification, etiology, compensation mechanisms, clinical and laboratory manifestations.

Acidosis is a violation of the acid-base balance, characterized by the appearance in the blood of an absolute or relative excess of acids and an increase in the concentration of hydrogen ions

1) Gas acidosis
2) Non-gas acidosis

- metabolic acidosis
- excretory acidosis
- exogenous acidosis

Gas acidosis (Figure 11.4) is a violation of the acid-base balance of the body, which is characterized by an increase in the content of carbon dioxide in the blood.

Etiology of gas acidosis

The main causes of gas acidosis are insufficiency of the function of external respiration (bronchospasm, pulmonary edema, depression of the respiratory center, etc.); decreased blood flow in the lungs (acute heart failure); excessive formation of carbon dioxide in the body that is not compensated by ventilation (fever, sepsis); high concentration of carbon dioxide in the inhaled air (being in poorly ventilated rooms).

Pathogenesis of gas acidosis

As a result of the above reasons, the partial pressure of carbon dioxide in the blood increases, hypercapnia and hypoxemia develop (a decrease in the partial pressure of oxygen). An increase in pCO_2 in the blood and intercellular fluid leads to an increase in the concentration of carbonic acid in them and an increase in the concentration of hydrogen ions. Excess carbon dioxide is eliminated from the body by the respiratory system due to an increase in the number of respiratory movements (tachypnea). The excess of hydrogen ions in the blood is compensated by protein and phosphate buffers, the processes of acidogenesis and ammoniogenesis increase in the kidneys, and the reabsorption of sodium bicarbonate increases, and the pH of the urine decreases.

Hypercapnia causes arterioles spasm in the organs, increases the total peripheral resistance of blood vessels, increases blood pressure, and bronchospasm develops in the lungs. Narrowing of the bronchi lumen is especially pronounced in their pathology (chronic bronchitis, bronchial asthma, lungs emphysema, etc.), the bronchi mucous membrane produces viscous mucus; which leads to an even greater narrowing of the bronchi and bronchioles lumen. Excess carbon dioxide in the blood leads to the expansion of the brain blood vessels, which is accompanied by an increase in intracranial pressure and an increase in the production of cerebrospinal fluid, headache.

With gas acidosis, the following changes in indicators are noted:

- blood pH value less than 7.35;
- pCO2 greater than 45 mmHg.

Non-gas acidosis (Figure 11.5) is a frequent and most severe form of acid-base state disorders. The basis for the development of non-gas acidosis is the accumulation of non-volatile acids in the body.

Etiology of non-gas acidosis

According to etiological factors, non-gas acidosis can be divided into three groups:

1) metabolic acidosis occurs when excessive accumulation of non-volatile acids in the body: diabetes mellitus, prolonged and intense muscle load, starvation;

2) excretory acidosis develops when there is a violation of the excretion of acidic substances as a result of impaired renal function (acute and chronic renal failure);

3) exogenous acidosis with excessive introduction of acids into the body (poisoning with acetic acid, salicylates).

Pathogenesis of non-gas acidosis

Neutralization of excess acidic products is possible due to their dilution with extracellular fluids. Mechanisms of compensation for non-gas acidosis include buffer and physiological systems of the body. Acids interact with bicarbonates, the content of bicarbonates in the blood decreases. The resulting carbonic acid is removed from the body during breathing. An important sign of metabolic acidosis is the stimulation of respiration associated with an increase in hydrogen ions. The breath becomes noisy and deep (Kussmaul's breath). In exchange for potassium ions, red blood cells receive hydrogen ions, and the concentration of potassium ions in the blood increases. Proteins exhibit alkaline properties. Acidogenesis and ammoniogenesis increase in the kidneys, while the reabsorption of bicarbonates increases. The pH of the urine decreases.

In non-gas acidosis, the following changes in indicators are noted:

- blood pH value less than 7.35;
- SB (standard bicarbonate) less than 22 mmol/l;
- BE (excess of buffer bases) less than 2.5 mmol/l.

Alkaloses. Classification, etiology, compensation mechanisms, clinical and laboratory manifestations.

Alkalosis is a violation of the acid-base balance, in which there is an absolute or relative increase in the number of bases and a decrease in the concentration of hydrogen ions

Alkalosis:

1. Gas alkalosis
2. Non-gas alkalosis
   - excretory alkalosis
   - exogenous alkalosis

Gas alkalosis (Figure 11.6) is a violation of the acid-base balance of the body, which is characterized by a decrease in the partial pressure of carbon dioxide in the blood.

Etiology of gas alkalosis

Gas alkalosis occurs during hyperventilation of the lungs as a result of the following conditions: hypoxia, overheating, hyperpyretic fever, violations of artificial ventilation of the lungs, stimulation of the respiratory center.

Pathogenesis of gas alkalosis

As a result of all these reasons, the removal of CO_2 from the body exceeds the rate of its formation. Hypocapnia causes a decrease in peripheral vascular tone and a decrease in blood pressure. An important mechanism for compensating for hypocapnia is a decrease in the excitability of the respiratory center, which leads to a reduction in breathing (bradypnea) and a delay of CO_2 in the body. Hydrogen ions are mixed into red blood cells in exchange for extracellular potassium ions, hyperkalemia develops. The consequence of hypokalemia is a violation of the heart rhythm, intestinal paresis, convulsions. The protein buffer exhibits acidic properties. In the renal tubules, the secretion of hydrogen ions compensatingly decreases, the formation of ammonia is inhibited and the excretion of bicarbonate increases. The urine pH increases.

With gas alkalosis, the following changes in indicators are noted:

- the pH value of the blood is more than 7.45;
- pCO_2 less than 35 mmHg.

Non-gas alkalosis (Figure 11.7) develops with an absolute or relative increase in the amount of alkaline compounds in the body.

Etiology of non-gas alkalosis

According to etiological factors, non-gas alkalosis can be divided into two groups:

1) excretory alkalosis develops with excessive excretion of acidic substances from the body as a result of impaired kidney function or through the gastrointestinal tract;

2) exogenous alkalosis with excessive introduction of alkaline compounds into the body.

Pathogenesis of non-gas alkalosis

Mechanisms of compensation for non-gas alkalosis include buffer and physiological systems of the body. Compensatory mechanisms are aimed at the formation of carbonic acid. The excitability of the respiratory center decreases, the breathing is reduced and the CO_2 content in the blood increases. Red blood cells give up hydrogen ions in exchange for potassium ions, hypokalemia develops. In the kidneys, the secretion of hydrogen ions and ammoniogenesis is limited, the excretion of bicarbonates increases, and the pH of the urine increases.

Clinical manifestations are associated with hypokalemia, changes in neuromuscular excitability: weakness of skeletal muscles, decreased motor activity of the gastrointestinal tract. Metabolic alkalosis is characterized by increased reflex reactions and the development of tetany as a result of a decrease in the concentration of calcium ions in the blood.

With non-gas alkalosis, the following changes in indicators are noted:

- blood pH value is more than 7.45;
- SB (standard bicarbonate) more than 26 mmol/l;
- BE (excess of buffer bases) more than 2.5 mmol/l

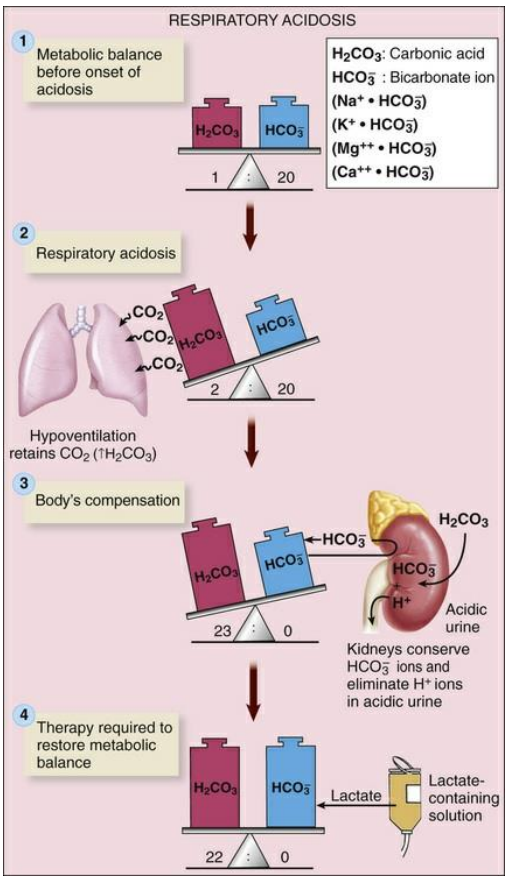

Figure 11.4 Respiratory acidosis with compensation and correction. *

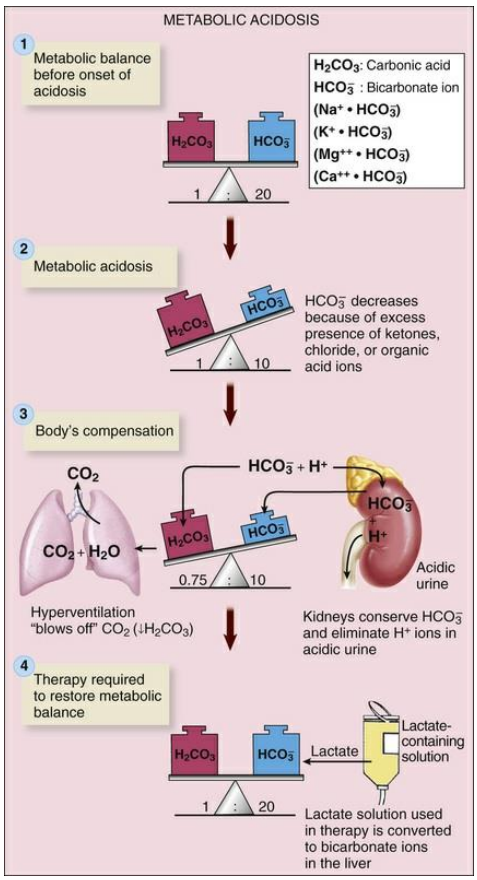

Figure 11.5 Metabolic acidosis with compensation and correction. *

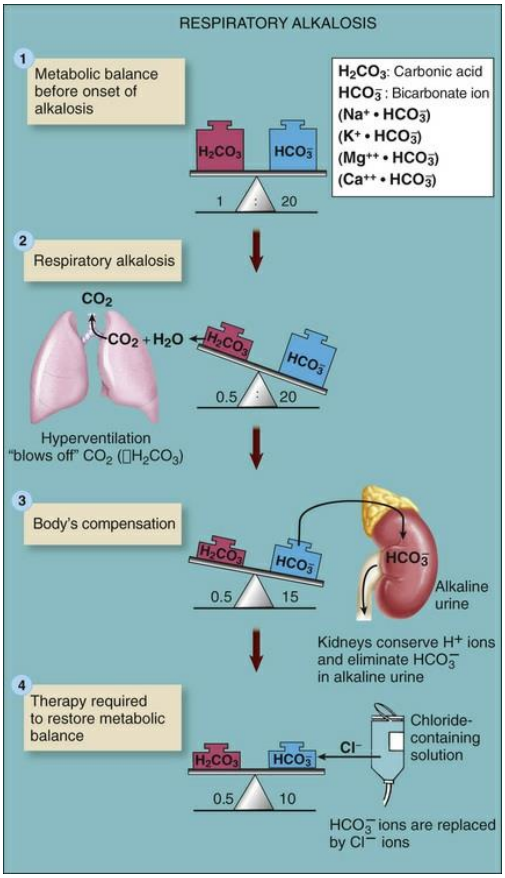

Figure 11.6 Respiratory alkalosis with compensation and correction. *

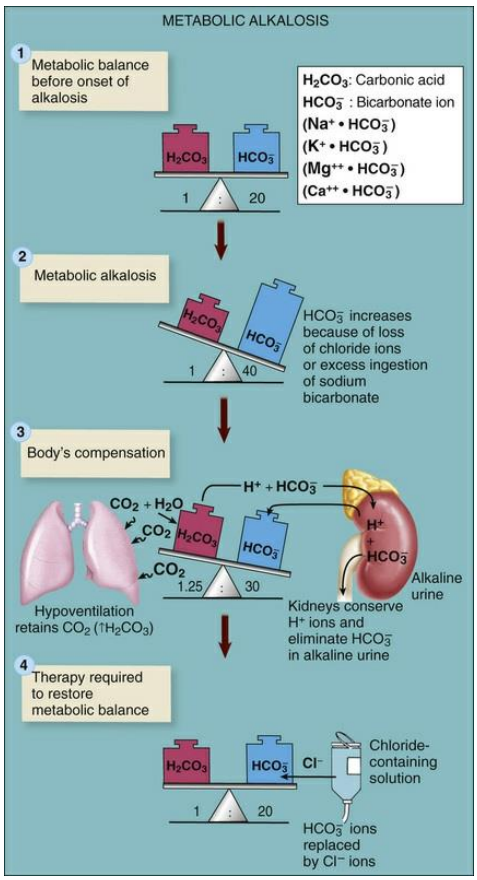

Figure 11.7 Metabolic alkalosis with compensation and correction. *

* (From Patton KT, Thibodeau GA: Anatomy & physiology, ed 9, St Louis, 2016, Mosby.)

Practical lesson 12. Pathophysiology of metabolism. Water exchange disorders. Oedemata.

Key questions of the session

1. The balance of water in the body, the mechanisms of its regulation. Classification of violations of water exchange.
2. Hypohydration: classification, etiology, pathogenesis, compensation mechanisms.
3. Hyperhydration: classification, etiology, pathogenesis, compensation mechanisms.
4. Edema: definition of the concept, types, pathogenesis.
5. Pathogenesis of edema in heart failure.
6. Pathogenesis of edema in nephrotic syndrome.
7. Pathogenesis of inflammatory, hungry and hepatic edema.

The balance of water in the body, the mechanisms of its regulation. Classification of violations of water exchange

Water makes up about 65% of body weight, which indicates the important role of water in the human body. The water content in the body of men is higher than that of women, which is associated with a large amount of adipose tissue in women. There is an external water balance and an internal water balance in the body. External water balance is the balance of water between water intake and excretion of water from the body. Internal water balance is the distribution of water in the body across sectors. Water in the body is divided into sectors: intracellular and extracellular. The intracellular sector makes up 40% of the body weight; extracellular - 25% of body weight.

The extracellular sector includes: interstitial **water** - 15% of body weight, plasma - 5% of body weight, lymph - 2% of body weight, transcellular fluid - 3% of body weight (cerebrospinal and articular fluid, pleural fluid, intraocular fluid and etc.). Water content in the body is associated with age. The total water content in newborns is higher and amounts to 75-80% of the body weight (extracellular sector 25-30%). As the body ages, the water content decreases.

About 2.5 liters of water enter the human body per day, of which: 1.2 liters enter the body with drinking and liquid food, 1 liter comes with solid food. As a result of metabolism in the body, 0.3 liters of endogenous water is formed. The body maintains a constant internal volume of water due to obligatory water losses, the volume of which is also 2.5 liters. Obligatory water losses include renal and extrarenal losses. Renal losses are 1.5 liters. Extrarenal losses are the excretion of fluid through the gastrointestinal tract - 0.1 liters, with perspiration - 0.5 liters and through the respiratory tract - 0.4 liters.

The regulation of the BCC is provided by the following mechanisms: a change in the glomerular filtration rate, a change in the activity of the renin-angiotensin-aldosterone system (RAAS), sodium uretic factor, intrarenal kinin and prostaglandin systems. The glomerular filtration rate depends on the BV. With a decrease in the BV, the blood flow in the kidneys decreases, the glomerular filtration rate and diuresis, therefore, the BV is restored.

The triggering factors for the activation of the RAAS are: a decrease in blood flow through the renal arteries, activation of the sysmpatoadrenal system through β-adrenergic receptors in the juxtaglomerular renal apparatus (JUA), an increase in sodium concentration in primary urine. As a result of these influences, the secretion of renin by the kidney JUA cells increases, the enzyme renin acts on angiotensinogen and angiotensin I is formed from it. When blood passes through the lungs, angiotensin II is formed from angiotensin I under the action of an angiotensin-converting enzyme. All angiotensins are vasoconstrictors, angiotensin II increases the secretion of aldosterone, which retains sodium and water in the body. BV increases accordingly. Sodium uretic factor enhances natriuresis and is a functional antagonist of the RAAS, which leads to a decrease in BV.

Plasma osmolality is regulated through the thirst center located in the third ventricle and directly through the antidiuretic hormone synthesized in the hypothalamus. An increase in plasma osmolality, a decrease in BCC is a stimulus for the synthesis of ADH.

Classification of water balance disorders:

Hypohydration:

- hypoosmolar (plasma osmolality more than 295 mosmol / l)
- isoosmolar (plasma osmolality 275 - 295 mosmol / l)
- hyperosmolar (plasma osmolality less than 275 mosmol / l)

Hyperhydration:

- hypoosmolar (plasma osmolality more than 295 mosmol / l)
- isoosmolar (plasma osmolality 275 - 295 mosmol / l)

- hyperosmolar (plasma osmolality less than 275 mosmol / l)

From the suffering water sector:

- intracellular hypohydration or overhydration
- extracellular hypohydration or overhydration
- mixed hypohydration or overhydration

Hypohydration: classification, etiology, pathogenesis, compensation mechanisms

Hypohydration is a typical pathological process, characterized by a negative water balance, while the loss of water exceeds the flow of water and the formation of water in the body

Hyperosmolar hypohydration is characterized by predominant water loss, while electrolyte losses are minimal. This condition occurs when the flow of fluid into the body is limited (violation of the swallowing process, damage to the esophagus, violation of the feeding regime of young children) or with an increase in water loss from the body (diabetes insipidus, prolonged fevers). As a result of all these reasons, the osmotic pressure of the blood plasma increases and the fluid moves into the vascular bed from the intercellular space and cells. Thus, the cells lose water and cellular dehydration develops. Hyperosmolar hypohydration is manifested by excruciating thirst, dry skin and mucous membranes, and an increase in body temperature.

Compensation mechanisms: a decrease in the glomerular filtration rate, an increase in the activity of the renin-angiotensin-aldosterone system, the onset of thirst, an increase in the secretion of ADH.

Isoosmolar hypohydration is characterized by an equivalent loss of water and electrolytes. Isoosmolar hypohydration develops with acute blood loss or plasma loss, with polyuria, with profuse diarrhea. As a result of these reasons, the BCC decreases, the minute volume of blood decreases, blood pressure and central venous pressure fall.

Compensation mechanisms: a decrease in the glomerular filtration rate, an increase in the activity of the renin-angiotensin-aldosterone system, the onset of thirst, an increase in the secretion of ADH.

Hypoosmolar hypohydration is characterized by predominant loss of electrolytes. Hypoosmolar hypohydration develops with prolonged and profuse sweating, in the presence of intestinal or stomach fistulas, with prolonged vomiting, diarrhea, with the development of hypoaldosteronism. In these conditions, predominant losses of electrolytes from the body occur, which is accompanied by a decrease in the osmotic pressure of the plasma, and water moves from the vascular bed into the intercellular space and then into the cells. Cellular overhydration occurs, cerebral edema develops, which is manifested by the development of convulsive syndrome.

Compensation mechanisms: a decrease in the glomerular filtration rate, an increase in the activity of the renin-angiotensin-aldosterone system.

Hyperhydration: classification, etiology, pathogenesis, compensation mechanisms

Hyperhydration is a typical pathological process characterized by a positive water balance, while water intake and water formation in the body exceed water losses

Hyperosmolar hyperhydration is characterized by an increase in water and electrolytes in the body, but mainly the content of electrolytes increases. Hyperosmolar hyperhydration occurs when drinking seawater, with inadequate administration of hypertonic solutions, or when the elimination of electrolytes from the body is limited (hyperaldosteronism, tubular nephropathy). In these cases, the osmotic pressure in the plasma increases, water moves into the vessels from the intercellular space and cells. Cells lose water and cellular dehydration occurs. BV increases, blood pressure rises, heart overload occurs, pulmonary and cerebral edema develops.

Compensation mechanisms: increased glomerular filtration rate, increased formation of natriuretic peptide, thirst, increased secretion of ADH.

Isoosmolar hyperhydration is characterized by an equivalent increase in body water and electrolytes. Isoosmolar hyperhydration develops with an overdose of isotonic solutions, blood transfusions, heart failure. Under the influence of the etiological factor, the hydrostatic pressure in the vessels increases, water moves into the intercellular space, which is manifested by the development of peripheral edema, pulmonary and cerebral edema. In addition, blood pressure rises, myocardial overload with blood volume develops.

Compensation mechanisms: increased glomerular filtration rate, increased formation of natriuretic peptide.

Hypoosmolar hyperhydration is characterized by a predominant increase in the water content in the body. Hypoosmolar overhydration develops with an increased intake of water into the body (for example, when drinking distilled water, overdose of hypotonic solutions) or when the excretion of water from the body is limited (increased production of antidiuretic hormone, renal failure). As a result of an increase in water in the body, the osmotic pressure of blood plasma decreases and water moves into the intercellular space and then into the cells, cellular hyperhydration develops, which is manifested by cerebral edema.

Compensation mechanisms: increased glomerular filtration rate, increased formation of natriuretic peptide.

Edema: definition of the concept, types, pathogenesis

Edema is the accumulation of fluid in the intercellular space and / or in body cavities as a result of impaired water exchange in the body.

Classification of edema according to the leading factor of pathogenesis:

- hydrodynamic factor
- oncotic factor
- osmotic factor
- membranogenic factor
- lymphogenous factor

The hydrodynamic factor is associated with an increase in the hydrostatic pressure in the vessels, which occurs with an increase in the volume of circulating blood or with a local increase in venous pressure, for example, in violation of the outflow of blood from the microcirculation system, thrombosis, embolism, compression of venules.

The oncotic factor is associated with a decrease in oncotic pressure in the vascular bed. A decrease in oncotic blood pressure is the result of a decrease in protein-synthetic processes in the liver, increased protein losses in kidney pathology, or a restriction of protein intake from food.

The osmotic factor is associated with an increase in osmotic pressure in the intercellular space, for example, during inflammation, hypoxia, acidosis.

The membrane factor is associated with an increase in the permeability of the vascular wall, which is observed under the action of inflammatory mediators or leukocyte enzymes, or under the action of endotheliotropic microorganisms. For example, swelling with inflammation.

Lymphogenous factors are the result of a violation of lymph outflow or the result of increased lymph production. For example, elephantiasis in parasitic diseases.

Pathogenesis of edema in heart failure. Pathogenesis of edema in nephrotic syndrome.

Pathogenesis of inflammatory, hungry and hepatic edema.

Edema may be inflammatory or noninflammatory. Inflammation-related edema accumulate due to increases in vascular permeability caused by inflammatory mediators. Usually, inflammation-associated edema is localized to one or a few tissues, but in systemic inflammatory states, such as sepsis, that produce widespread endothelial injury and dysfunction, generalized edema may appear, often with severe consequences. In contrast, noninflammatory edema is protein-poor fluids called transudates. Noninflammatory edema is common in many diseases, including heart failure, liver failure, renal disease, and severe nutritional disorders (Figure 12.1).

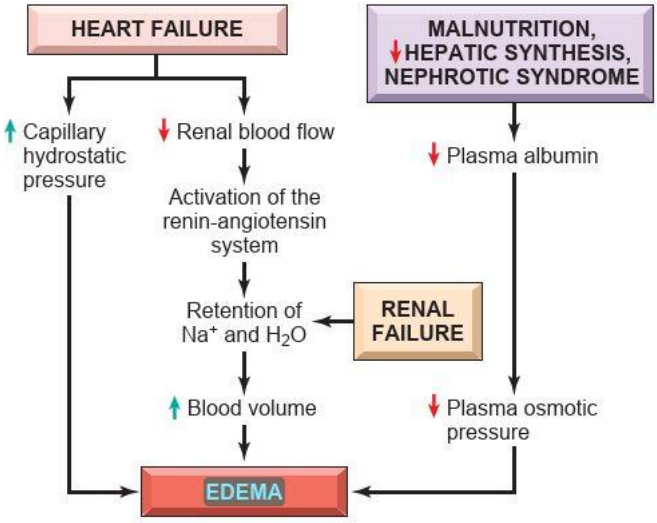

Figure 12 .1 Mechanisms of systemic edema in heart failure, renal failure, malnutrition, hepatic failure, and nephrotic syndrome. (Data from Robbins and Cotran pathologic basis of disease:115, 2015.)

The generalized edema in nephrotic syndrome is a direct consequence of decreased intravascular colloid osmotic pressure. There is also sodium and water retention, which aggravates the edema. This seems to be due to several factors, including compensatory secretion of aldosterone, mediated by the hypovolemia-enhanced renin secretion; stimulation of the sympathetic system; and a reduction in the secretion of natriuretic factors such as atrial peptides. Edema is characteristically soft and pitting, and is most marked in the periorbital regions and dependent portions of the body. If severe, it may also lead to pleural effusions and ascites.

One of the most important causes of renal hypoperfusion is congestive heart failure, which (like hypoproteinemia) results in the activation of the renin-angiotensin-aldosterone axis. In early heart failure, this

response is beneficial, as the retention of sodium and water and other adaptations, including increased vascular tone and elevated levels of antidiuretic hormone, improve cardiac output and restore normal renal perfusion. However, as heart failure worsens and cardiac output diminishes, the retained fluid merely increases the hydrostatic pressure, leading to edema.

Pathogenesis of hepatic edema. The accumulation of excess fluid in the peritoneal cavity is called ascites. In 85% of cases, ascites is caused by cirrhosis. Ascites usually becomes clinically detectable when at least 500 mL have accumulated. The fluid is generally serous, having less than 3 gm/dL of protein (largely albumin), and a serum to ascites albumin gradient of ≥1.1 gm/dL. The fluid may contain a scant number of mesothelial cells and mononuclear leukocytes. Influx of neutrophils suggests infection, whereas the presence of blood cells points to possible disseminated intra-abdominal cancer. With long-standing ascites, seepage of peritoneal fluid through trans-diaphragmatic lymphatics may produce hydro-thorax, more often on the right side. The pathogenesis of ascites is complex, involving the following mechanisms:

1. Sinusoidal hypertension, altering Starling's forces and driving fluid into the space of Disse, from where it is removed by hepatic lymphatics; this movement of fluid is also promoted by hypoalbuminemia.
2. Percolation of hepatic lymph into the peritoneal cavity: Normal thoracic duct lymph flow approximates 800 to 1000 mL/day. With cirrhosis, hepatic lymphatic flow may approach 20 L/day, exceeding thoracic duct capacity. Hepatic lymph is rich in proteins and low in triglycerides, which explains the presence of protein in the ascitic fluid.
3. Splanchnic vasodilation and hyperdynamic circulation. These conditions were described earlier, in relationship to the pathogenesis of portal hypertension. Arterial vasodilation in the splanchnic circulation tends to reduce arterial blood pressure. With worsening of the vasodilation, the heart rate and cardiac output are unable to maintain the blood pressure. This triggers the activation of vasoconstrictors, including the renin-angiotensin system, and also increases the secretion of antidiuretic hormone. The combination of portal hypertension, vasodilation, and sodium and water retention increases the perfusion pressure of interstitial capillaries, causing extravasation of fluid into the abdominal cavity.

Practical lesson 13. Pathophysiology of metabolism. Disorders of carbohydrate metabolism: hypo - and hyperglycemic conditions. Diabetes mellitus

Key questions of the lesson

1. Hypoglycemic conditions: types, development mechanisms, significance for the body. Hypoglycemic coma.
2. Hyperglycemic conditions: types, development mechanisms, significance for the body.
3. Diabetes mellitus: definition, classification, criteria. The action mechanism of insulin.
4. Insulin-dependent diabetes mellitus: etiology, pathogenesis.
5. Insulin-independent diabetes mellitus: etiology, pathogenesis.
6. Diabetes mellitus: pathogenesis of manifestations, prevention and therapy principles.
7. Diabetic comas: ketoacidotic, hyperosmolar, lacticacidemic. Etiology, pathogenesis, manifestations.

Carbohydrates in the human body perform an important function, being a source of energy. Normally, the blood glucose content is 3.3-5.5 mmol/l. The regulation of carbohydrate metabolism is provided by insulin and counterinsular hormones. The counterinsular hormones are glucagon, somatotropic hormone, catecholamines, and cortisol.

Classification of carbohydrate metabolism disorders

1. Hypoglycemia
   - physiological
   - alimentary
   - pathological
2. Hyperglycemia
   - physiological
   - pathological

Hypoglycemia is a condition in which the blood glucose level is less than 3.3 mmol/l. Physiological hypoglycemia develops after prolonged physical exertion or after prolonged psychoemotional stress. Alimentary hypoglycemia is the result of limiting the intake of glucose from food (fasting). Pathological hypoglycemia occurs with hyperinsulinism, an overdose of insulin, a decrease in glucose synthesis in the body, or with increased glucose loss as a result of kidney disease.

Hyperglycemia is a condition in which the blood glucose level is greater than 5.5 mmol/l. Physiological hyperglycemia develops after eating a meal containing a large amount of carbohydrates, with bulimia. Pathological hyperglycemia develops in a number of disorders in the body, for example, inflammation, infections, endocrine disorders, the use of drugs, a decrease in the synthesis of insulin or its effects.

Diabetes mellitus is a syndrome that occurs as a result of absolute or relative insulin deficiency, characterized by a violation of all types of metabolism, primarily carbohydrate, manifested by hyperglycemia, glucosuria polyuria and other symptoms

Criteria for diabetes mellitus (WHO, 2011)

- the level of glycated hemoglobin is more than 6.5%;
- fasting glycemia greater than 7 mmol/l;
- positive glucose tolerance test

Classification of diabetes mellitus

- type 1 diabetes mellitus;
- type 2 diabetes mellitus;
- diabetes mellitus of pregnant women;
- symptomatic diabetes mellitus

Type 1 diabetes mellitus (insulin-dependent diabetes) (Figure 11.1) it is approximately about 5-10% of all forms of diabetes mellitus. Diabetes mellitus 1 develops mainly at a young age, it is not characterized by gender differences, it develops mainly in people with normal or even low body weight. Diabetes mellitus 1 develops acutely, often manifesting ketoacidotic coma. The etiological factors of diabetes mellitus 1 are environmental factors (viruses, chemicals) and hereditary factors. Coxsackie viruses, mumps, measles, measles rubella, and cytomegaloviruses activate white blood cells via Toll-like receptors, which is accompanied by increased interferon secretion and expression of HLA antigens on the β-cell membrane, which are recognized by lymphocytes. Chemicals: alloxan, food cyanides, cow's milk proteins (bovine serum albumin), cyanides, nitrosamines. The development of insulin-dependent diabetes is based on autoimmune reactions: cell-mediated

(type IV hypersensitivity reactions) and humoral. Under the influence of viruses or chemicals, the presentation of autoantigens on the surface of β-cells occurs, followed by the development of insulitis and the destruction of β-cells. Factors of destruction of β-cells are: IL-1, TNF-alpha, IFN-gamma, CD8+ lymphocytes, autoantibodies, reactive oxygen species from macrophages, neutrophils.

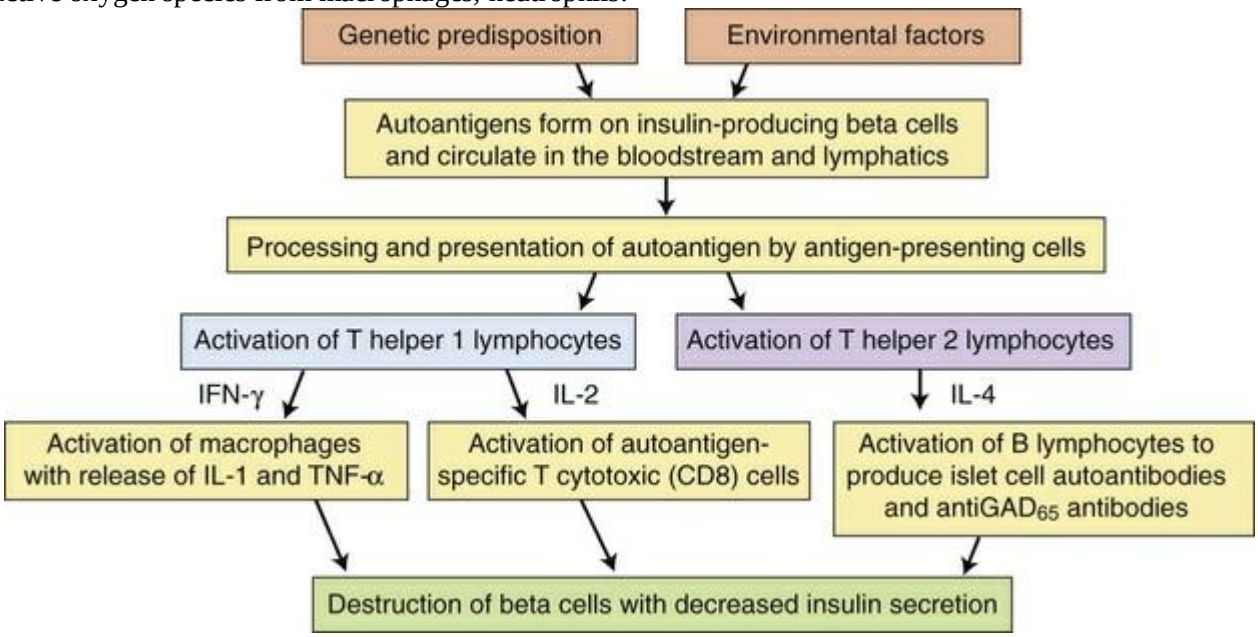

Figure 11.1 Pathophysiology of Type 1 Diabetes Mellitus. GAD_{65}, Glutamic acid decarboxylase; IFN-γ, interferon-gamma; IL, interleukin; TNF-α, tumor necrosis factor-alpha. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Type 2 diabetes mellitus (insulin-independent diabetes) is approximately about 90-95% of all forms of diabetes mellitus. Type 2 diabetes mellitus develops mainly after 40 years, more often in women and people with increased body weight, develops gradually. The type 2 diabetes development is associated with a hereditary predisposition and the presence of risk factors. Risk factors are gender, age, overweight, hypodynamia, prolonged negative psychoemotional effects, atherosclerosis, arterial hypertension, etc. In the pathogenesis of type 2 diabetes mellitus (Figure 13.2), insulin resistance and β-cell dysfunction are important. Insulin resistance of insulin-dependent tissues is associated with the inability of cells to respond to the insulin action. This is the result of either a decrease in the receptors number, or violations of the post-receptor transmission of the insulin signal. The basis of β-cell dysfunction is the discrepancy between the need for insulin and its production for the realization of its effects in cells under conditions of insulin resistance and hyperglycemia. Factors of β-cell decompensation are an increase in the concentration of glucose and free fatty acids in the blood.

The main diabetes symptoms are hyperglycemia, polydipsia, and polyuria. The development of hyperglycemia is associated with impaired glucose uptake by cells. Hyperglycemia leads to the appearance of glucose in the urine, and glucosuria develops. Glucose is an osmotically active substance, which leads to the development of polyuria and, as a result, thirst increases and polydipsia develops (Figure 13.3).

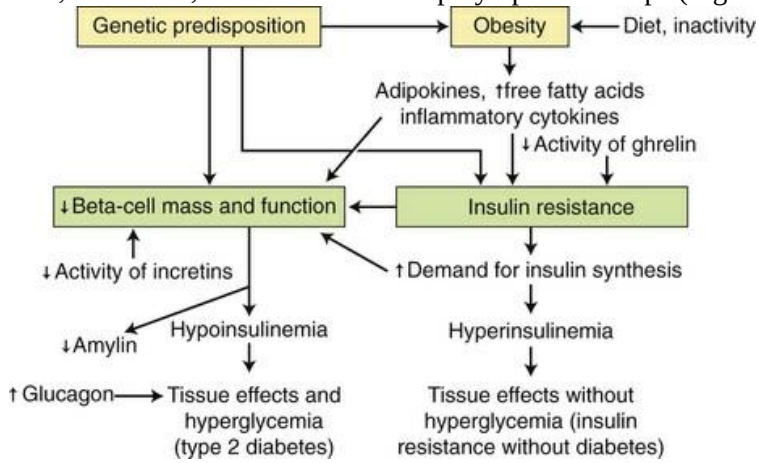

Figure 13.2 Pathophysiology of Type 2 Diabetes Mellitus. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

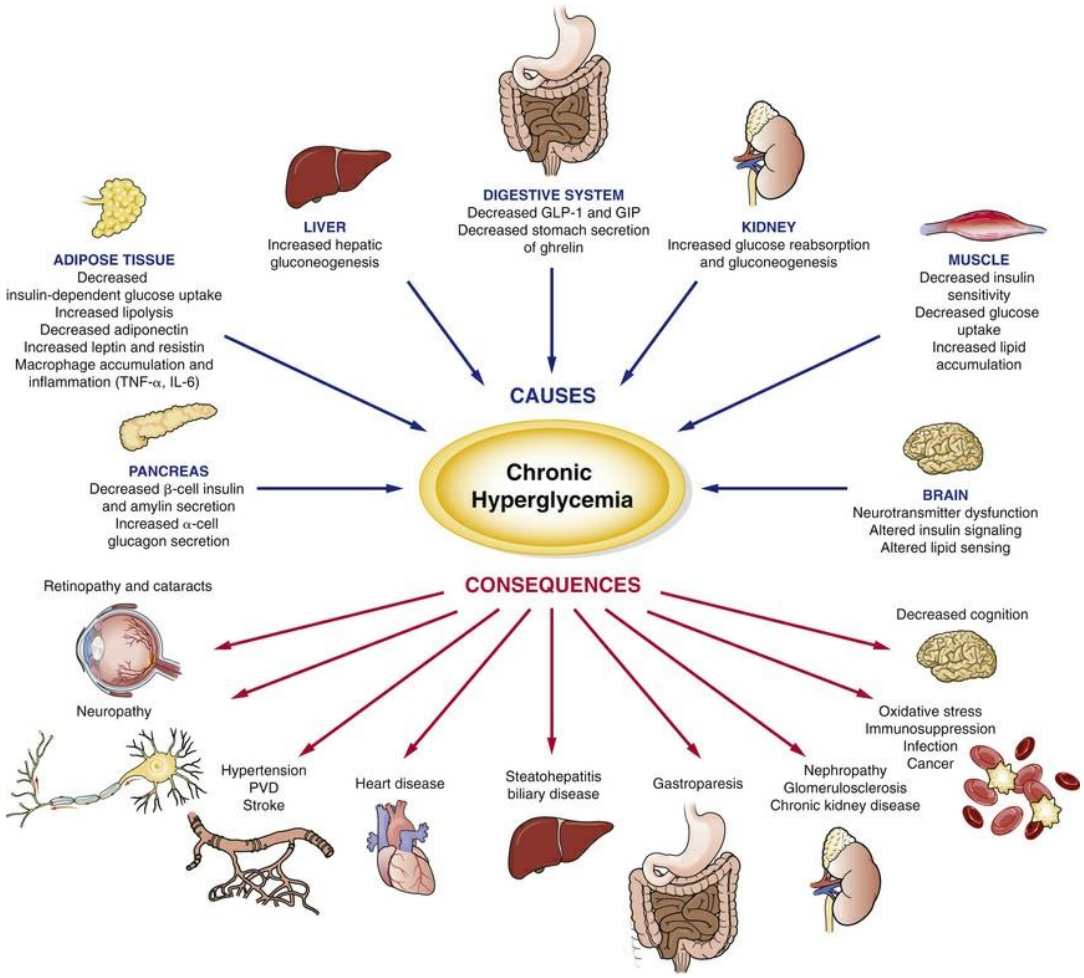

Figure 13.3 Multiorgan causes and common consequences of chronic hyperglycemia in type 2 diabetes mellitus. GIP, Gastrifc inhibitory peptide; GLP-1, glucagon-like peptide-1; IL, interleukin; PVD, peripheral vascular disease; TNF, tumor necrosis factor. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Acute complications of diabetes mellitus are comas: ketoacidotic, hyperosmolar, lactoacidotic, hypoglycemic.

Ketoacidotic hyperosmolar coma (Figure 13.4) develops in type 1 diabetes mellitus, the coma is characterized by ketosis and ketoacidosis. The trigger factor is an increase in the production of contrinsular hormones and an increase in the processes of lipolysis. Increased production of contrinsular hormones leads to the development of hyperglycemia, increased lipolysis, accompanied by the ketone bodies accumulation and the acidosis development. Hyperglycemia is accompanied by polyuria and a decrease in VCB, hemoconcentration occurs and hemic hypoxia develops. In addition, hyperglycemia increases the plasma osmolality, cell dehydration develops, the skin and mucous membranes are dry, the eyeballs tone is reduced. As a result of dehydration, the central nervous system neurons functions are disrupted, there is a loss of consciousness, areflexia, Kussmaul's breathing occurs, the acetone smell in the exhaled air is characteristic.

Hyperosmolar non-ketoacidotic coma (Figure 13.4) develops in type 2 diabetes mellitus. Risk factors for developing hyperosmolar non-ketoacidotic coma are dehydration, such as vomiting, diarrhea, and drinking disorders. The main pathogenesis link is an increase in plasma osmolality as a result of hyperglycemia, cell dehydration, circulatory hypoxia, including neuronal hypoxia, develops. Hyperosmolar coma develops gradually, over several days, characterized by symptoms of polydipsia, polyuria, drowsiness, deafness.

Lactoacidotic coma develops in type 2 diabetes mellitus. Risk factors for developing a coma are excessive physical activity, respiratory tract infections, and heart failure. As a result of these reasons, hypoxia of neurons develops. The development of hypoxia leads to the activation of anaerobic glycolysis and the lactate accumulation. The development of coma is manifested by apathy, drowsiness, loss of consciousness, the appearance of Kussmaul's breath, but there is no acetone smell in the exhaled air.

Hypoglycemic coma develops with an insulin overdose or glucose consumption increase by tissues. Glucose is the main energy source for brain cells, so there is a lack of energy and the functions of CNS cells are disrupted. The coma development is manifested by a hunger feeling, anxiety, tachypnea, tachycardia develops.

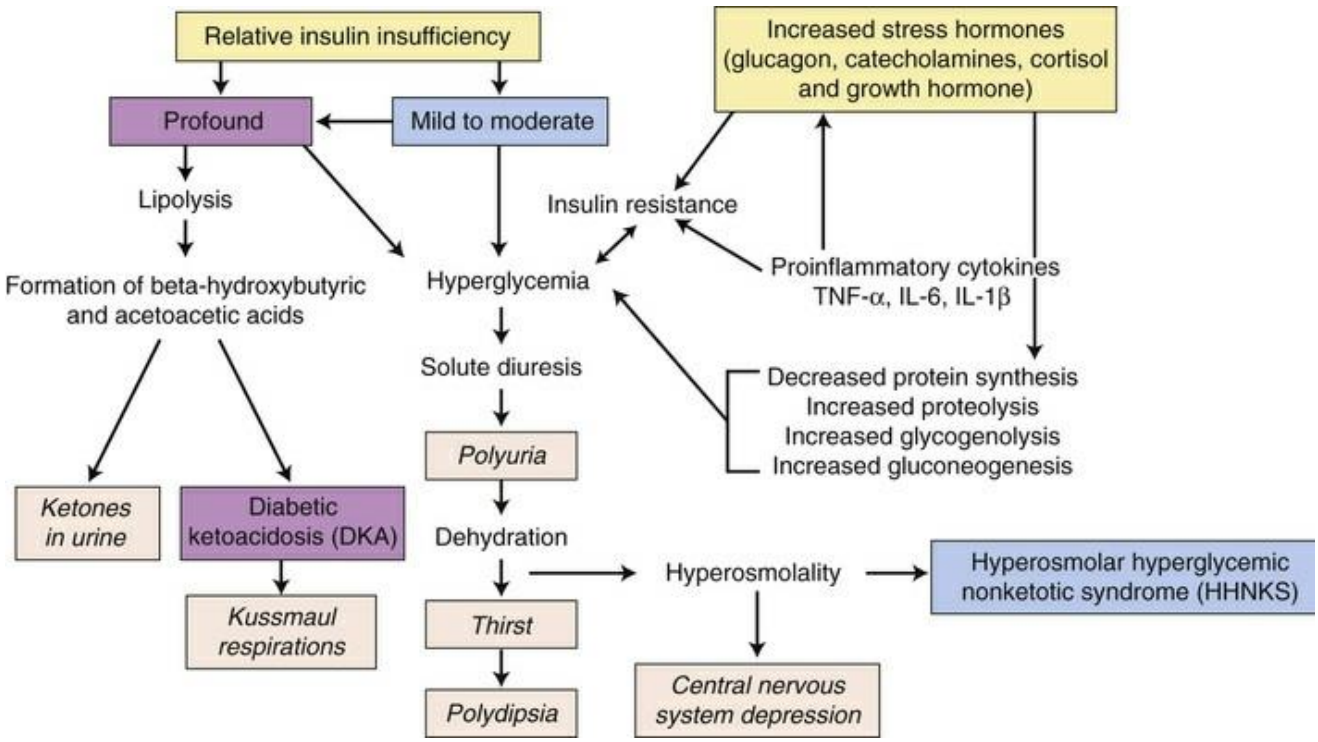

Figure 13.4 Pathophysiology of DKA and HHNKS in Diabetes Mellitus. DKA, Diabetic keto-acidosis; HHNKS, hyperosmolar hyperglycemic non-ketotic syndrome; IL-6, interleukin-6; IL-1β; interleukin-1beta; TNF-α, tumor necrosis factor-alfa. (Inserts from K.L. McCance et al: Pathophysiology. The biologic basis for Disease in adults and Children, ed 8, Salt Lake City, 2019, Elsevier.)

Practical lesson 14. Pathophysiology of tumor growth

Key questions of the session

1. Tumor growth: definition of the concept. Benign and malignant tumors.
2. Etiology of tumors: physical, chemical, biological carcinogens.
3. Stage of initiation in carcinogenesis. The role of epigenomic changes. The concept of protooncogenes, anti-oncogenes and their products.
4. Stage of promotion in carcinogenesis. Tumor atypism and its types.
5. Tumor progression: mechanisms and consequences. Mechanisms of invasive growth and metastasis. Types of metastasis.
6. Antiblastoma resistance of the organism: immune and non-immune factors.

Tumor growth: definition of the concept. Benign and malignant tumors

Tumor growth is a typical pathological process, arises in response to the action of carcinogens, is characterized by dysfunction of genes that control cell proliferation (protooncogenes and anti-oncogenes), manifested by irreversible changes in the processes of growth, differentiation and maturation of cells

Table 14.1 Comparative characteristics of benign and malignant tumors

Indication	Benign tumor	Malignant tumor
Growth	Expansive. Slow. No metastasis.	Invasive. Quick. With metastasis.
Cell differentiation	High.	Low. The lower differentiation, the more malignant tumor is.
Maturation of cells	The cells are more mature. Tissue atypism may develop.	The cells are less mature. Cellular and tissue atypism develops.
Prediction	Favorable, if the tumor does not affect vital organs.	Adverse. Fatal without treatment.

Tumor diseases of the maxillofacial region account for 2-4% of the total number of human tumor diseases. By origin, tumors of the maxillofacial region are divided: odontogenic, which develop from hard tissues (enamel, dentin, bone tissue), and non-odontogenic, developing from epithelium, connective tissue, muscles.

Etiology of tumors: physical, chemical, biological carcinogens

The etiological factor of tumors is a carcinogen.

A carcinogen is a factor, the effect of which on the human or animal body increases the risk of malignant tumors.

By nature, carcinogens are divided into three groups:

1. Chemical carcinogens
2. Physical carcinogens
3. Biological carcinogens

Chemical carcinogens

By the mechanism of action, chemical carcinogens are divided into three groups:

1. Direct acting carcinogens are true carcinogens. They themselves change the structure of the cell's DNA. Example: lactones, chloroethylamines, epoxybenzanthracene.
2. Carcinogens of indirect action (pre-carcinogens). Metabolized to form free radicals that change the structure of the cell's DNA. This is how most chemical carcinogens act.
3. Promoters of carcinogens - stimulate the action of a carcinogen. Example: phenobarbital, croton oil.

By origin, chemical carcinogens are classified into the following groups:

1. Polycyclic hydrocarbons (anthracene derivatives). Examples of substances: benzopyrene, petroleum and coal refined products, tobacco sublimation products. Participate in the development of tumors of the trachea, bronchi, lungs, nasopharynx, larynx, esophagus.
2. Aromatic amines (aniline derivatives). Examples of substances: colorants, preservatives, insecticides. Lead to the development of tumors of the bladder, kidney, liver.
3. Nitroso compounds (nitrosamines, nitrosamides, formed from nitrites). Examples: substances used in the production of plastics, preservatives, medicines. Lead to the development of tumors of the gastrointestinal tract, liver, kidneys.

4. Derivatives of benzene (xylene, toluene). Examples: substances used in rubber, paint and varnish, leather, pharmaceutical production, gasoline, solvents, varnishes, paints. Lead to the development of tumors of hematopoietic tissue (leukemia).

5. Asbestos (silicates Mg, Fe, Na). Leads to the development of tumors of the pleura, peritoneum, lungs, stomach, uterus.

6. Medicines. Examples: cytostatics, immunosuppressants, phenacetin. Lead to the development of tumors: hematopoietic tissue, lymphatic system, hepatobiliary system, kidney, bladder.

7. Endogenous chemical carcinogens. Examples: bile metabolites, sex hormones, reactive oxygen species.

Physical carcinogens

1. Infrared radiation (heat). Tumors may develop at the site of permanent burns in stokers, glassblowers, cooks.

2. Ultraviolet radiation. Ultraviolet radiation with a wavelength of 280-315 nm has a carcinogenic effect. Risk factors: being in regions with ozone holes, low skin pigmentation.

Ultraviolet waves are absorbed by DNA molecules, knocking out electrons from DNA atoms, as a result of which free radicals are formed, which contribute to the neoplastic transformation of cells.

3. Ionizing radiation. It is subdivided into several types depending on the type of particles and penetrating ability: alpha - radiation, beta - radiation, gamma - radiation, X-ray radiation.

To assess the carcinogenic effect, the penetrating ability of various types of ionizing radiation is important. Any dose of radiation is biologically dangerous, but the most dangerous is frequent exposure to small doses. Intensively proliferating tissues (hematopoietic, lymphoid, sex glands, epithelial tissue) are affected more than others.

Biological carcinogens

Biological carcinogens include DNA and RNA-containing oncoviruses. The consequences of the interaction of the virus and the cell can be different:

1. Cell cytolysis after virion replication.

2. Latent infection (incomplete replication at the stage of the introduction of the virus into the genome), which can lead to indifferent or lethal mutations, as well as to mutations in cell growth genes, accompanied by neoplastic cell transformation.

DNA-containing oncoviruses include the following types of viruses:

1. Family of herpes viruses (Herpesviridae): type 4 - Epstein-Barr virus, causes Burkitt's lymphoma, nasopharyngeal carcinoma, other types of herpes viruses cause Kaposi's sarcoma, cervical cancer.

2. The family of papillomaviruses (Papillomaviridae) causes cervical cancer, laryngeal cancer.

3. The hepatnavirus family - hepatitis B virus, is important in the development of hepatitis B and liver cancer.

The mechanism of carcinogenic action. DNA viruses contain promoter genes, which, after being inserted into the genome of a cell, can:

• activate cellular protooncogenes (oncogenes - inducers of cell growth and reproduction);

• suppress the activity of cellular anti-oncogenes (anti-oncogenes - blockers of cell growth and reproduction)

RNA-containing oncoviruses include the following types of viruses:

1. Human T-cell lymphoma virus (HTLV-1)

2. Hepatitis C virus (Hepatit C virus HCV).

The mechanism of carcinogenic action is due to the presence of the v-onc virus and genes of promoters and enhancers in the genome.

1. Due to the presence in the genome of v-onc (viral analogs of cellular protooncogenes), which are incorporated into the DNA of the target cell and enhance the activity of cellular protooncogenes.

2. Due to the presence of genes in the genome of the virus - promoters and enhancers, which are incorporated into the DNA of the target cell and enhance the activity of cellular protooncogenes.

In advanced primary carcinomas, cancer cells recruit a variety of cell types into the surrounding stroma, including fibroblasts, myofibroblasts, granulocytes, macrophages, mesenchymal stem cells, and lymphocytes (Fig 14.1)

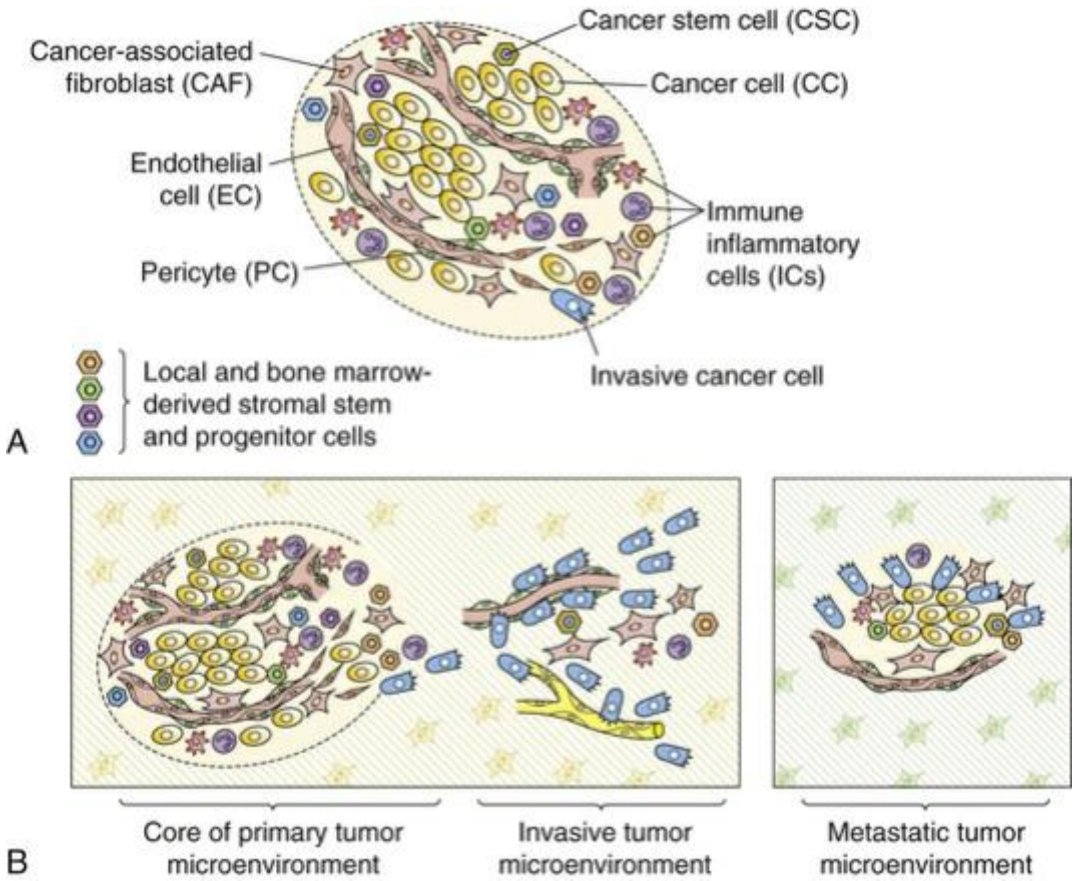

Figure 14.1 Cells of the Tumor Microenvironment. A, Distinct cell types constitute most solid tumors including breast tumors. Both the main cellular tissue, called parenchyma, and the surrounding tissue, or stroma of tumors, contain cell types that enable tumor growth and progression. For example, the immune-inflammatory cells present in tumors can include both tumor-promoting and tumor-killing subclasses of cells. B, The microenvironment of tumors. Multiple stromal cell types create a succession of tumor microenvironments that change as tumors invade normal tissue, eventually seeding and colonizing distant tissues. The organization, numbers, and phenotypic characteristics of the stromal cell types and the extracellular matrix (hatched background) evolve during progression and enable primary, invasive, and metastatic growth. (Not shown are the premalignant stages.) (Data from Hanahan D, Weinberg R: Cell 144:646–674, 2011.)

Stage of initiation in carcinogenesis. The role of epigenomic changes. The concept of protooncogenes, anti-oncogenes and their products

Pathogenesis: three stages are distinguished in the development of malignant tumors (Fig 14.2):

1.stage initiation

2. stage of promotion

3. stage of tumor progression.

Initiation stage. At the initiation stage, the formation of a tumor genotype occurs as a result of the activation of protooncogenes and / or a decrease in the activity of anti-oncogenes. The mechanisms of these processes are: point mutations, translocations, amplification, transfection, or epigenomic changes. The formation of epigenomic changes is facilitated by oxidative stress, damage to protein molecules, environmental factors, age, and diet disorders.

Oncogenes encode the synthesis of oncoproteins (growth factors, receptors for growth factors, post-receptor growth factors) or proteins that inhibit apoptosis. Anti-oncogenes encode the synthesis of proteins that prevent cell growth: cell cycle breakers, G-protein blockers, DNA repairs, adhesive molecules.

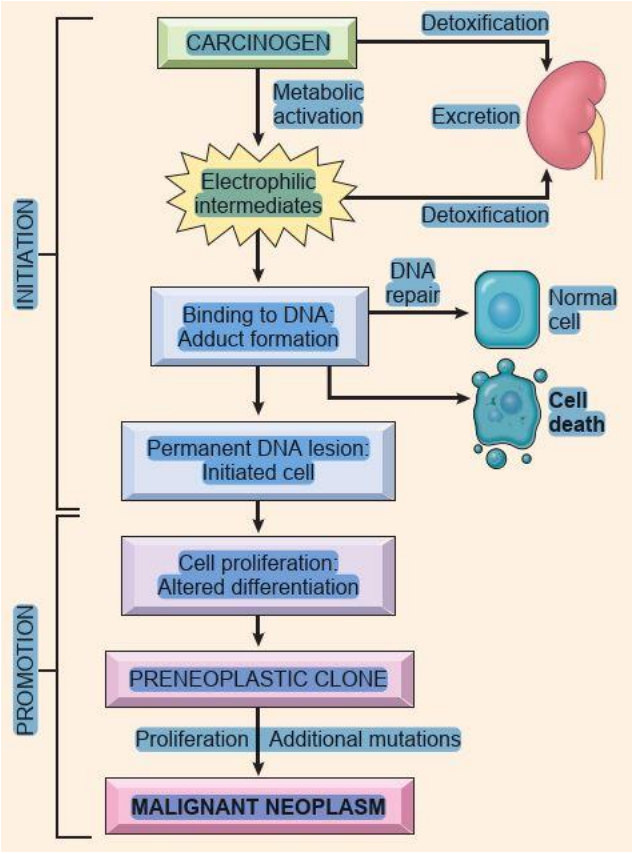

Figure 14.2 General schema of events in chemical carcinogenesis. Note that promoters cause clonal expansion of the initiated cell, thus producing a preneoplastic clone. Further proliferation induced by the promoter or other factors causes accumulation of additional mutations and emergence of a malignant tumor. (Data from Robbins and Cotran pathologic basis of disease:322, 2015.)

Stage of promotion in carcinogenesis. Tumor atypism and its types

Promotion stage. In the stage of promotion, a tumor phenotype is formed, which is manifested by cellular and tissue atypism. Cellular atypism includes: genetic atypism, biochemical atypism, immunological atypism. Genetic atypism of cells of malignant neoplasms is characterized by a change in nuclear-cytoplasmic relations due to an increase in the proportion of the nucleus, polyploidy, chromosomal aberrations and mutations are possible. Biochemical atypism is characterized by a change in all types of metabolism. The main source of energy for tumor cells is anaerobic glycolysis. Tumor cells consume glucose faster and more efficiently, so cancer cells are susceptible to hypoglycemia. For cells of malignant neoplasms, the negative Pasteur effect is characteristic. In the cells of a malignant tumor, the synthesis of DNA and RNA increases, the tumor cell synthesizes its own protein molecules, for example, embryonic proteins, alpha-fetoprotein, etc. are synthesized. These features of protein metabolism ensure the rapid proliferation of tumor cells. At the same time, cancer cells are able to consume large amounts of certain amino acids, creating a deficiency of these amino acids in the body. Thus, protein synthesis is disrupted and inhibited in the body. In addition, malignant tumor cells consume large amounts of fatty acids and cholesterol, which leads to a decrease in lipid storage in the body. These changes lead to depletion of the body and the development of cachexia.

Tissue atypism of malignant tumors is manifested by the loss of contact inhibition, the loss of the Hayflick limit, the acquisition of the property of immortalization (immortality). The life cycle of a normal cell includes apoptosis, programmed cell death. Normal cells in the body go through several cycles of division and then die. Malignant tumor cells can divide indefinitely, both in the body and outside the body.

Tumor progression: mechanisms and consequences. Mechanisms of invasive growth and metastasis. Types of metastasis

The stage of tumor progression is characterized by a change in the properties of tumor cells towards an increase in their viability and a variety of properties (Fig 14.3). Cells with a new genotype and phenotype appear as a result of spontaneous and induced mutations, the tumor becomes polyclonal. There is a selection of more viable cells, that is, the tumor evolves. Selection occurs as a result of the influence of factors of the immune system, treatment, competition of malignant tumor cells for substrates, oxygen, and place.

The consequences of tumor progression are: escape of the tumor from the action of factors of the immune system, the emergence of resistance to therapy, invasive growth and metastasis. Invasion is the ability of a malignant tumor to grow into surrounding tissues, that is, a malignant tumor extends beyond the area intended for this tissue (Fig 14.4). In this case, the destruction of the surrounding tissues occurs and it is impossible to determine the boundaries of the malignant tumor, which significantly complicates the surgical removal of the malignant tumor. The cells of a malignant tumor can break away from the main focus and be carried throughout the body by blood and lymph. Then they settle in distant organs and form secondary foci of tumor growth, metastases. The process of metastasis is carried out in several stages (Fig 14.5). Initially, the cells of a malignant tumor adhere to the vessel, then the process of intravasation into a lymphatic or blood vessel occurs, a tumor embolus is formed, followed by extravasation. Most often, metastases are formed in the lungs, liver, lymph nodes.

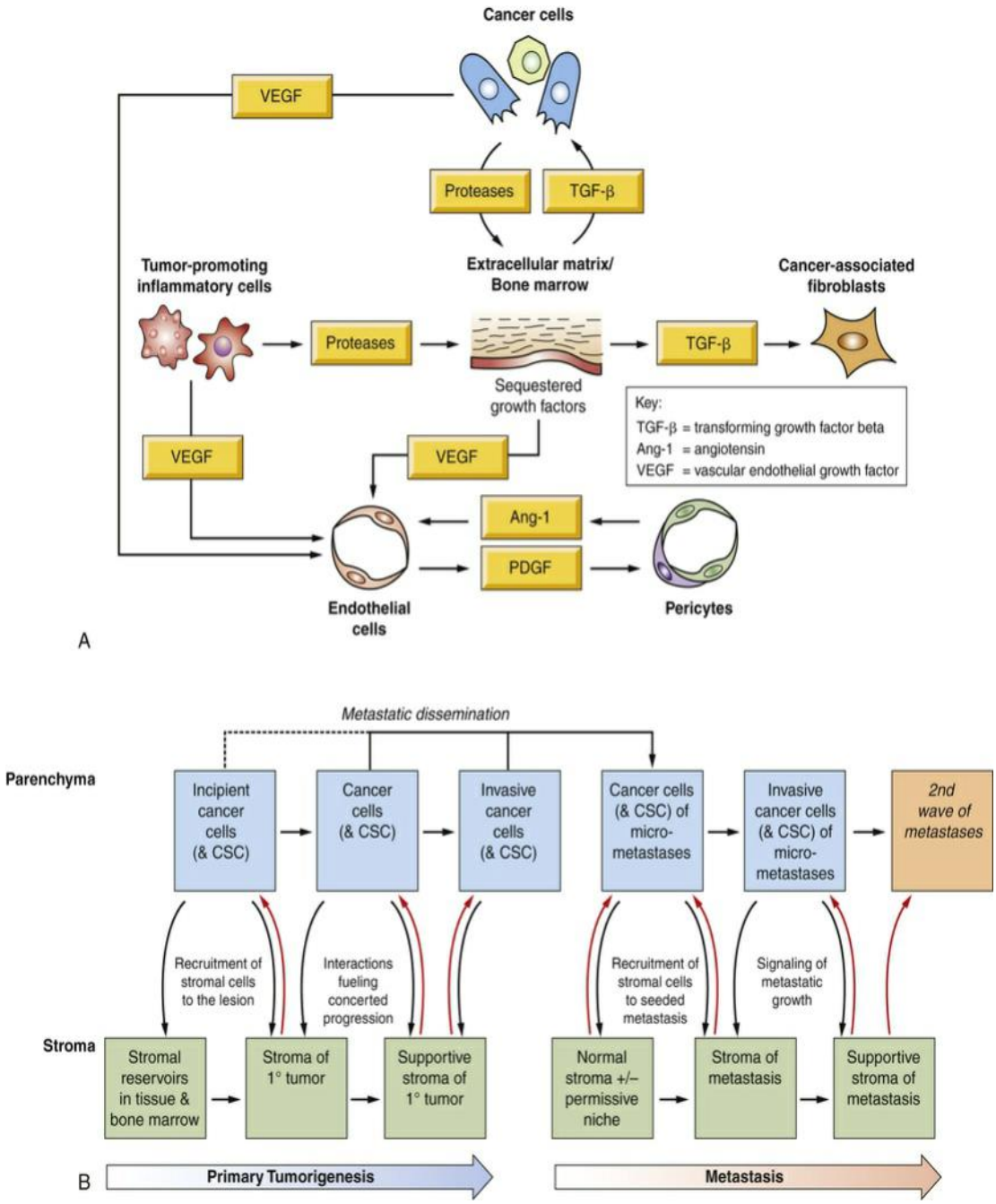

Figure 14.3 Signaling Interactions in the Tumor Microenvironment During Malignant Progression. A, Numerous cell types constitute the tumor microenvironment and are orchestrated and maintained by reciprocal interactions. B, The reciprocal interactions between the breast main tissue or parenchyma and the surrounding stroma are important for cancer progression and growth. Certain organ sites of "fertile soil" or "metastasis niches" facilitate metastatic seeding and colonization. Cancer stem cells are involved in some or all stages of tumor

development and progression. CSC, Cancer stem cells. (Adapted from Hanahan D, Weinberg R: Cell 144:646–674, 2011.)

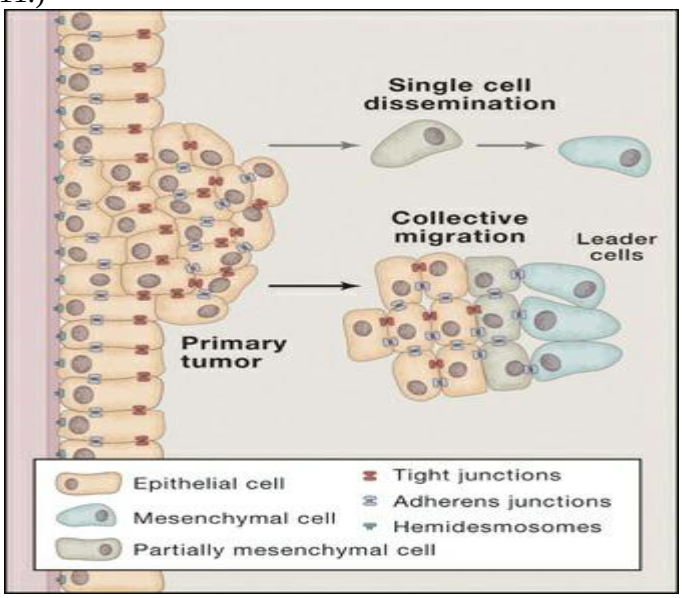

Figure 14.4 Invasion. Invasion of carcinoma cells occurs through two mechanisms: single cell dissemination through an epithelial-mesenchymal transition (EMT) (gray arrow), or the collective dissemination of a tumor cluster of cells. Emerging evidence suggests that the leader cells of tumor groups or clusters undergo EMT-associated phenotypic changes. Clusters of migrating cells are commonly noted at the borders of invasive carcinomas and are best documented in breast and lungs. (Adapted from Lambert AW, Pattabiraman DR, Weinberg RA: Cell 168[4]:670–691, 2017.)

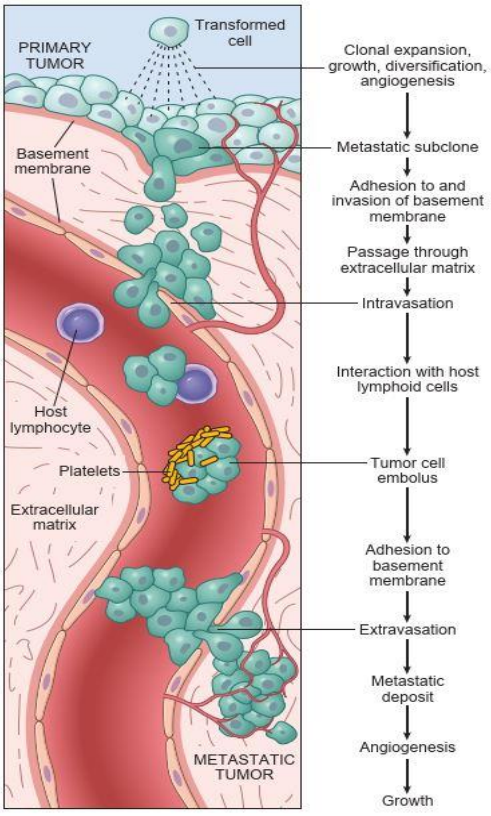

Figure 14.5 The metastatic cascade. Sequential steps involved in the hematogenous spread of a tumor.

Practical lesson 15. Pathophysiology of metabolism. Disorders of macro and microelement metabolism

Key questions of the lesson

1. Violation of sodium metabolism: etiology, pathogenesis and clinical manifestations.
2. Violation of potassium metabolism: etiology, pathogenesis and clinical manifestations.
3. Violation of calcium metabolism: etiology, pathogenesis, clinical manifestations.
4. Violation of phosphorus metabolism: etiology, pathogenesis, clinical manifestations.
5. Violation of magnesium metabolism: etiology, pathogenesis, clinical manifestations.

Violation of sodium metabolism: etiology, pathogenesis and clinical manifestations.

Sodium is the main plasma electrolyte, the normal concentration of sodium in the blood is 135-150 mmol/l, it depends on the content of proteins, lipids, and glucose in the plasma. Sodium is the only electrolyte that is added to food under physiological conditions, and sodium is excreted through the kidneys. Sodium is involved in the formation of the body's alkaline reserve, action potential, and potentiates the action of epinephrine. Sodium metabolism is regulated by aldosterone (increases the sodium reabsorption in the distal renal tubules), sodium-uretic hormone. There are the following disorders of sodium metabolism: **hypernatremia and hyponatremia**.

Hypernatremia is a pathological condition characterized by the sodium content increase in the blood above 150 mmol/l. The main cause of absolute hypernatremia is excessive sodium intake from food, sodium retention in the body with hyperaldosteronism, and hemoconcentration. Relative hypernatremia develops when the body exceeds the loss of pure water or water with a low content of electrolytes. With hypernatremia, arterial hypertension, cellular dehydration develops, which is manifested by an increase in neuromuscular excitability.

Hyponatremia is a pathological condition that occurs when the blood sodium content decreases to less than 135 mmol/l. Absolute hyponatremia occurs with a decrease in sodium intake from food, increased sodium loss through the kidneys, gastrointestinal tract, skin, with a decrease in sodium reabsorption in the distal renal tubules in hypoaldosteronism. Relative hyponatremia occurs when the extracellular fluid is diluted with excess water (hemodilution). Hyponatremia is accompanied by the development of cellular hyperhydration and is manifested by a decrease in blood pressure and the development of muscle weakness.

Violation of potassium metabolism: etiology, pathogenesis and clinical manifestations.

Potassium is the main cell space electrolyte, takes part in the formation of the resting potential and the action potential. The normal blood potassium content is 3.3-5.5 mmol/l. There are the following disorders of potassium metabolism: **hyperkalemia and hypokalemia** (Figure 15.1).

Hyperkalemia is characterized by an increase in the potassium content in the blood of more than 5.5 mmol/l. The causes of hyperkalemia are extensive injuries, internal bleeding, acidosis, insulin deficiency, and hypoaldosteronism. Hyperkalemia is a life-threatening condition, as it is accompanied by cardiac arrest in diastole. Hyperkalemia is manifested by pain in the muscles of the tongue, limbs, and abdomen; the development of muscle paralysis, and intestinal atony.

Hypokalemia is characterized by a decrease in the blood potassium content of less than 3.3 mmol/l. Hypokalemia develops with vomiting, diarrhea, hyperaldosteronism, alkalosis, hyperinsulinism, stress. Manifestations of hypokalemia are cardiac disorders, the development of paralysis of skeletal muscles or paralytic intestinal obstruction.

Violation of calcium metabolism: etiology, pathogenesis, clinical manifestations.

Calcium is a structural component of bones and teeth. Bones and teeth contain 99% of all the calcium in the body. Calcium also participates in the processes of blood clotting, connects the processes of nervous excitation and muscle contraction, provides the transmission of nerve impulses in chemical synapses, is a secondary intermediary, regulates the state of cell membranes. Calcium is involved in physiological processes only in ionized form. Normally, the calcium content in the blood is 2.2-2.5 mmol/l. Calcium is able to form strong compounds with proteins, phospholipids, and organic acids and is found in the blood in four fractions. It is a compound with proteins, a compound with lipids, acid-soluble and organic fractions. One-third of the calcium is bound to proteins, such as albumin, globulin. Disorders of calcium metabolism can be in the form of hypocalcemia and hypercalcemia (Figure 15.2). Hypocalcemia is more common.

Hypocalcemia is a condition in which the blood calcium content is less than 2.2 mmol/l. In children, the main cause of hypocalcemia is a deficiency of the active form of hypovitaminosis D. Other etiological factors of hypocalcemia are a decrease in the intake of calcium from food, impaired calcium absorption in chronic enteritis,

resection of small intestine fragments, chronic alkalosis, impaired reabsorption of calcium in the renal tubules, hypoparathyroidism, hypersecretion of calcitonin.

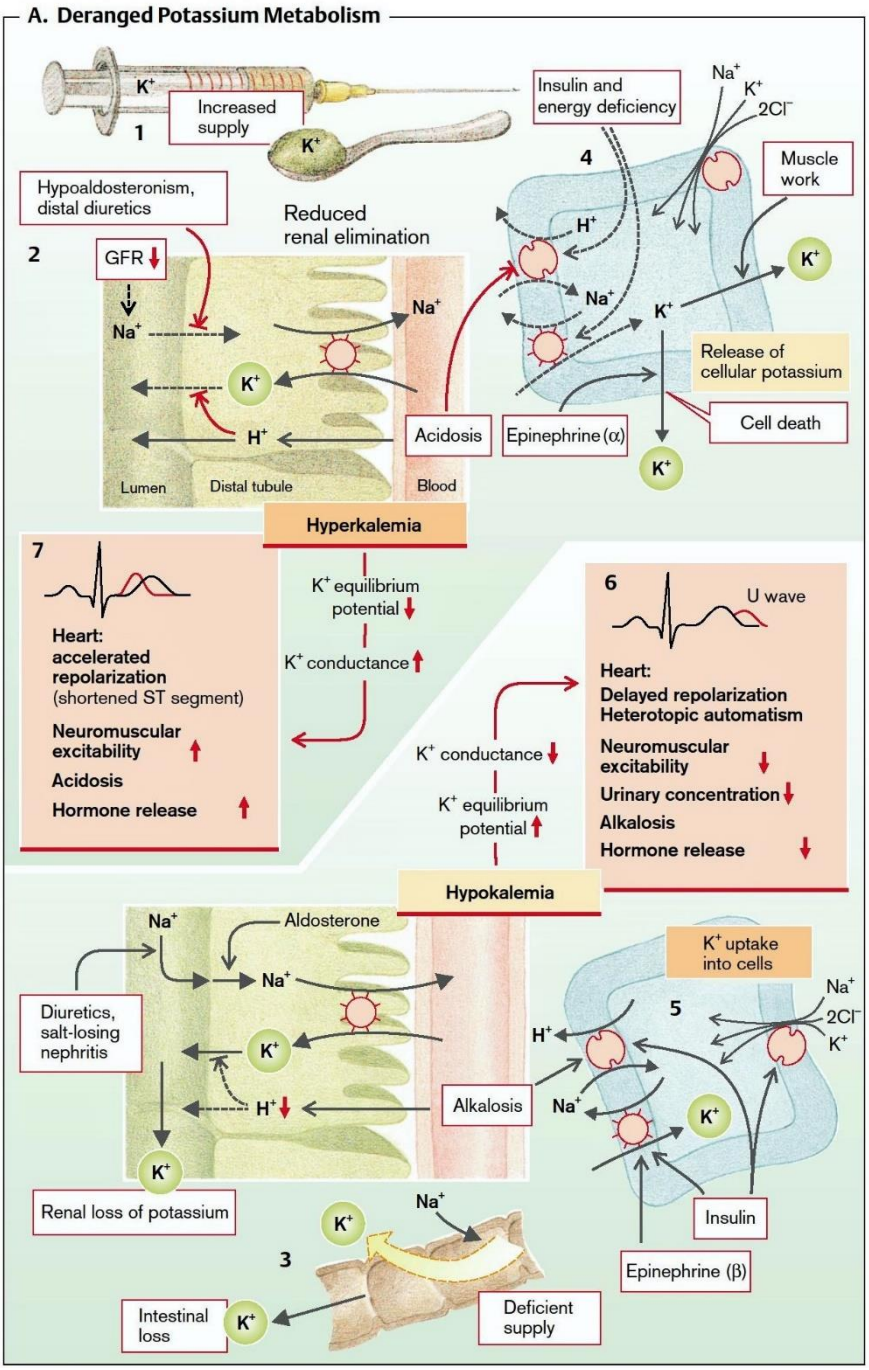

Figure 15.1 Abnormalities of Potassium Balance. GFR glomerular filtration rate (Inserts from S. Silbernagl, F. Lang: Color Atlas of Pathophysiology, 2 ed., New York, 2010, Thieme.)

Hypocalcemia is manifested by a neuromuscular excitability increase, there are attacks of spontaneous muscle contractions-tetanic convulsions of various muscle groups ("obstetrician's brush", symptoms of Chvostek and Trusso). With a decrease in the calcium content in the blood, hemorrhagic syndrome develops, blood pressure decreases, dystrophic changes in the tissues of ectoderm derivatives occur (dental defects, brittle nails and hair, dry skin), heart failure, osteoporosis develops.

Hypercalcemia is a pathological condition in which the calcium content in the blood is more than 2.5 mmol/l. Hypercalcemia is much less common and has a sluggish, low-symptom course. The most common cause of hypercalcemia is hypervitaminosis D. Hypercalcemia also develops with hyperfunction of the parathyroid glands, decreased calcitonin secretion, chronic acidosis, hypodynamia, weightlessness factors, and chronic renal failure.

Hypercalcemia is manifested by psychoneurological disorders (emotional instability, rapid fatigue, memory impairment), muscle hypotension and a decrease in neuromuscular excitability up to paresis and paralysis, the formation of kidney stones, osteoporosis (osteodystrophy).

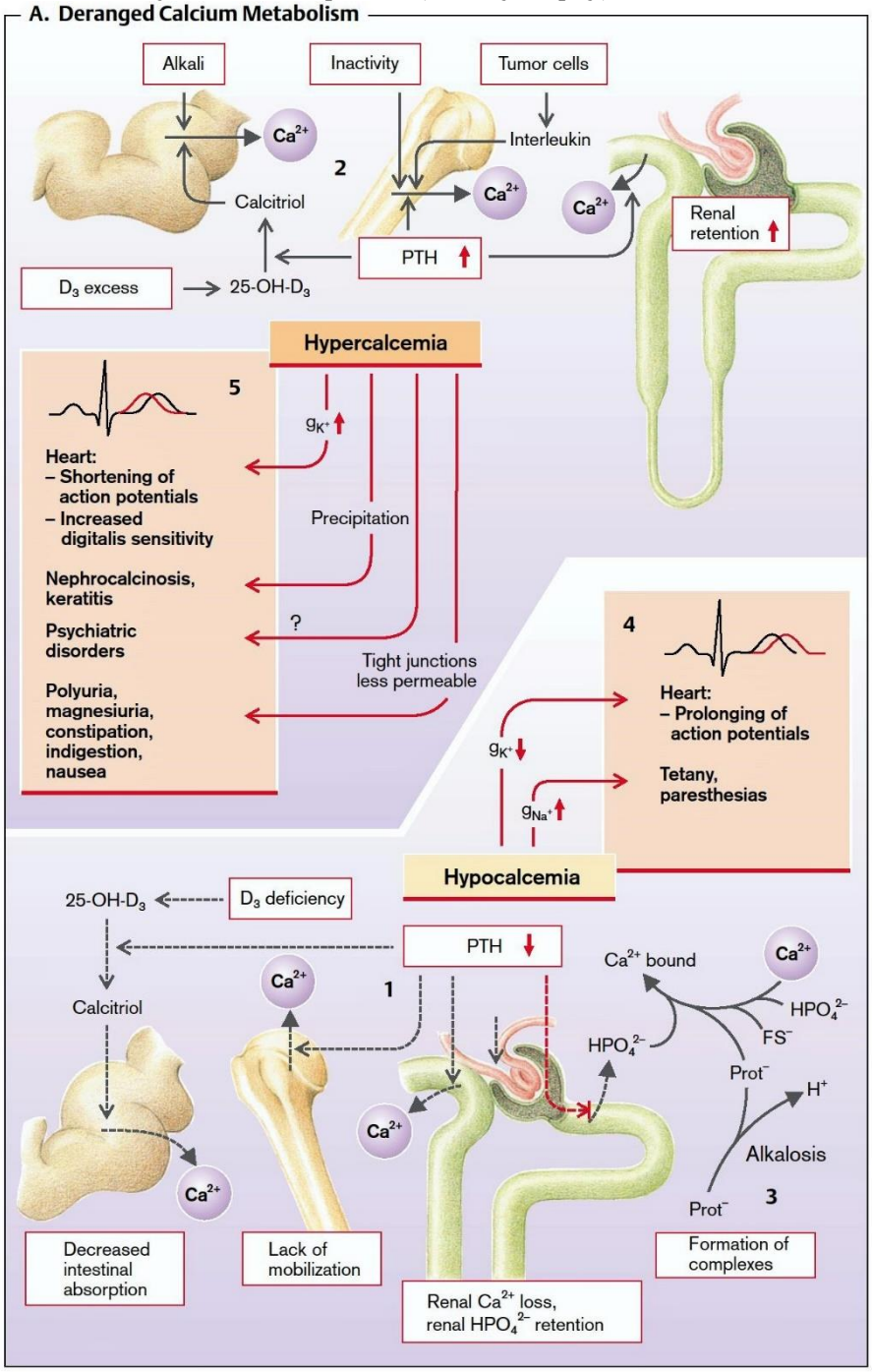

Figure 15.2 Abnormalities of Calcium Balance. (Inserts from S. Silbernagl, F. Lang: Color Atlas of Pathophysiology, 2 ed., New York, 2010, Thieme.)

Violation of phosphorus metabolism: etiology, pathogenesis, clinical manifestations.

Phosphorus is an element of macroergic compounds and their derivatives and, accordingly, plays an important role in the processes of metabolism and regulation of physiological functions. In the composition of minerals, phosphorus is included in the structure of bones and teeth, in which its content is up to 85%. Phosphorus in the composition of phospholipids is included in the structure of cell membranes, providing the fluid properties of cell membranes. Normally, the phosphorus content in the blood is 0.8-1.5 mmol/l. Disorders of phosphorus metabolism can be in the form of **hypophosphatemia and hyperphosphatemia** (Figure 15.3)**.**

Hypophosphatemia is a decrease in the phosphorus content in the blood of less than 0.8 mmol/l. Etiological factors of hypophosphatemia are a decrease in the intake of phosphorus from food, prolonged fasting,

impaired absorption of phosphorus in the gastrointestinal tract, hyperparathyroidism, loss of phosphorus in kidney pathology, glucosuria, alkalosis.

Hypophosphatemia is accompanied by a deficiency of ATP and is manifested by rapid fatigue, decreased performance, depression of the heart contractile function, muscle hypotension, hypoventilation, osteoporosis and osteomalacia.

Hyperphosphatemia is an increase in the phosphorus content in the blood of more than 1.5 mmol/l. The etiological factors of hyperphosphatemia are an increase in the intake of phosphorus into the body when administered intravenously or per os, hypoparathyroidism, phosphorus retention in the body in kidney pathology, increased production of somatotropic hormone, acidosis, cytolysis.

Hyperphosphatemia is manifested by arterial hypotension, arrhythmia, signs of hypocalcemia, deposition of calcium phosphate in soft tissues, joints, and blood vessels.

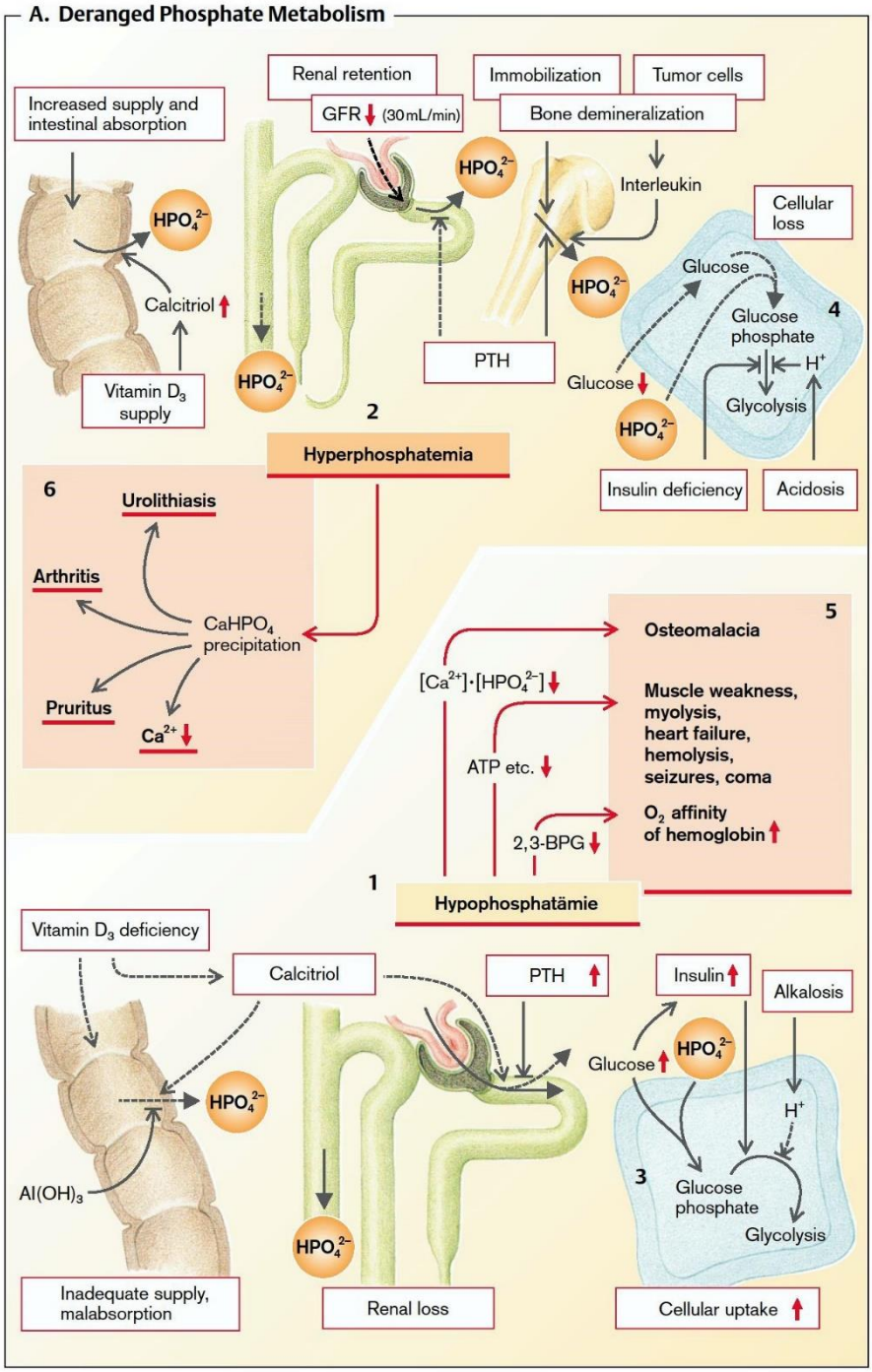

Figure 15.3 Abnormalities of Phosphorus Balance. (Inserts from S. Silbernagl, F. Lang: Color Atlas of Pathophysiology, 2 ed., New York, 2010, Thieme.)

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Osikov
Mikhail Vladimirovich

Ageeva
Anna Alekseevna

Savchuk
Ksenia Sergeevna

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тел.(351) 230-67-37; rinmed@mail.ru